TECHNICAL REPORT 8

POPULATION GENETICS AND HEALTH CARE ISSUES AND FUTURE STRATEGIES

राष्ट्रीय स्वास्थ्य एवं परिवार कल्याण संस्थान
NATIONAL INSTITUTE OF HEALTH
AND FAMILY WELFARE, NEW DELHI

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COMMUNITY HEALTH CEL

Population Genetics and Health Care
Issues and Future Strategies

Technical Report 8

POPULATION GENETICS AND HEALTH CARE ISSUES AND FUTURE STRATEGIES

Proceedings of the Workshop on Population Genetics and Health Care —March 24-27th, 1982

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Preface

Human Population Genetics is primarily concerned with the study of precise genetic composition of the populations and the various factors which ultimately determine the biological basis of health of populations. Untiring efforts of the Anthropologists, Human Biologists and other scientists in the field have generated large amount of data on the basic genetic polymorphisms (e.g. blood groups, serum proteins, ABH secretions in saliva etc.), distribution of the abnormal haemoglobins and G-6-PD deficiency, disease associations with genetic markers, consanguinity and its effects in different population groups. However, studies were confined to select few population groups and regions of the country.

With the advancement in medical sciences, man has been able to contain some of the infectious diseases as a result of which the genetic and genetico-environmental diseases are being increasingly recognised. The genetic diversity of the Indian population groups inhabiting widely varying geoclimatic and ecological conditions poses a challenge to the population geneticists in eliciting the causes of variations and delineation of the health hazards due to genetic and genetico-environmental interactions.

In this extremely complex situation, beyond the academic interests, very little attention has been paid to the proper utilisation of the knowledge in larger interests of the human beings. It is thus, imperative to examine whether the information available is dependable and comparable in terms of techniques and methodology and whether it is suitable, appropriate, adequate and applicable for use in preventive and promotive health care. Answers to these questions, I am sure will lead to understanding of the lacunae and constraints and will provide future directions for studies in Population Genetics. It may be possible to learn a few lessons as to what information and in what form will be of use for medical and health personnel, administrators and policy planners. In order to ensure wider interaction, a Workshop on, "Population Genetics and Health Care" was organised by the National Institute of Health & Family Welfare from March 24th-27th, 1982.

Intensive deliberations in the Workshop for four days on various aspects of Human

Population Genetics have brougth forth salient observations and recommendations which are addressed to the priority areas of research in Human Population Genetics and provide guidelines for approaches in such studies. I am sure these will be useful to the researchers, administrators and policy makers in directing their endeavours and resources in more meaningful manner, keeping in view the preventive and promotive aspects of health care of the population.

SOMNATH ROY
Director
National Institute of Health and Family Welfare
New Delhi

Keynote Speakers

Dr. P.K. Sukumaran	Tata Memorial Centre, Cancer Research Institute, Parel, Bombay.
Dr. Arvind J. Baxi	Seth G.S. Medical College, Blood Group Reference Centre, Parel, Bombay.
Dr. S.C. Tiwari	Department of Anthropology, Delhi University, Delhi.
Dr. N.K. Mehra	Cellular Immunology Unit, Department of Anatomy, All India Institute of Medical Sciences, New Delhi.
Dr. S.K. Basu	Department of Population Genetics and Human Development, National Institute of Health and Family Welfare, New Delhi
Prof. I.P. Singh	Department of Anthropology, Delhi University Delhi.
Sh. P. Padmanabha	Registrar General and Census Commissioner, Govt. of India, New Delhi.
Dr. S.S. Agarwal	Department of Medicine, Genetics Division, K.G. Medical College, Lucknow.
Dr. L.M. Ambani	Medical Genetics Unit, Institute of Research in Reproduction, Parel, Bombay.

Introductory Note

India is characterised by the presence of a large number of diverse population groups, endogamous castes, tribes and religious communities inhabiting different ecological settings. Human Population Genetics is primarily concerned with the study of genetic composition of the populations and various factors determining the prevalence of different genetic traits in them. The mating behaviour and changing environmental conditions profoundly influence the human gene pool and consequently the frequencies of different genetic constitutions which determine the biological basis of the health of populations. A fuller comprehension of human population genetics will lead to greater understanding of the complex interactions that have taken place in the past and that exist at present between man and his changing environment, and also of their implications for the health of future generations.

In March 1967, the first Workshop on Medical and Human Population Genetics was organized at the Central Family Planning Institute, one of the forerunners of the present Institute. During the past 15 years, a large number of studies carried out on different genetic aspects of population groups in India have generated good amount of data, but these have not been properly examined and assessed in the light of their relevance to national health care programme. There is an urgent need to review critically the present status of population genetic studies in India, identify the gaps in knowledge and to evaluate those genetic characteristics which could be fruitfully utilized for the preventive and promotive aspects of health care. Priority areas of research in Human Population Genetics having direct relevance to the promotion of health are to be delineated. It is time for population geneticists and health experts to join hands together for collecting meaningful genetic information by incorporating parameters on health indices, and socio-economic and cultural aspects. With this end in view, the workshop was organised.

Objectives

1 To review the present status of Population Genetic studies in India having relevance to the promotion of health.

2 Identification of priority areas of research in Human Population Genetics for promotion of health in the form of preventive care and other measures.

3 To identify active group of centres and investigators for organising collaborative multicentered studies on priority problems.

Participants

The participants of the workshop were drawn from various research institutions and universities who were actively engaged in research on various aspects of human population genetics as well as from health administrators, policy planners and personnel from census, Anthropological Survey of India and tribal research organisations.

Methodology

Six plenary sessions on various aspects of Human Population Genetics and Health Care were formed. Each plenary session was addressed at the beginning by a scientist actively engaged in that particular area of research. Each address was followed by discussions and clarifications.

Each plenary session was followed by group discussions on the theme of the session. Major emphasis was laid on group discussions to thrash out relevant observations and recommendations about the directions in which future research should be undertaken.

The participants were divided into two groups which met separately and deliberated in the light of the guidelines provided for each plenary session to formulate recommendations. The recommendations of the groups were synthesised by respective chairpersons and rapporteurs and were presented for final adoption. The final report embodying the accepted recommendations of the different plenary sessions was presented in the concluding session.

In his welcome address Prof. Somnath Roy, Director of the Institute, remarked that the quality of life was dependent upon the interactions between genetic endowment and environmental conditions, the latter being influenced by the physical, nutritional, socio-economic, cultural and other factors. Introducing the theme of the workshop, Prof. Roy raised certain vital issues pertaining to (a) proper utilisation of available information for preventive and promotive health care ; (b) need for dependable and comparable data in terms of techniques and methodology and (c) future collaborative multicentric studies by multidisciplinary groups, to be examined in the deliberations of the workshop.

Prof. H.D. Tandon, Director, All India Institute of Medical Sciences, New Delhi remarked in his inaugural address that the application of theory of Human Population Genetics to human welfare was full of possibilities so far as man's personal health and the future shaping of the society were concerned. Prof. Tandon drew attention to the increasing importance of diseases of genetic and genetico-environmental origin following the recent developments in the control of communicable and other diseases. He laid stress on the need for generating sound baseline data in Indian perspective on various genetic diseases (i.e. Haemoglobinopathies, G-6-PD deficiency, congenital malformations etc.) and the impact of consanguinity on health status in order to augment preventive and promotive aspects of health care.

Dr. P.K. Sukumaran introduced the subject of "Abnormal Haemoglobins in India —A Critical Appraisal with Particular Reference to Promotion of Health". Detailing the background information, he drew attention to the present state of knowledge with respect to Indian population groups, need for adopting uniform standardised methodology in the field and the importance of haemoglobinopathies in preventive health care.

Dr. A.J. Baxi in his keynote address on Glucose-6-Phosphate Dehydrogenase Deficiency in India emphasised upon the importance of G-6-PD Deficiency in view of the endemic nature of malaria in the country and highlighted the importance of clinical profile and drug sensitivity in G-6-PD deficient subjects, and its implications in health care.

Speaking on, "Blood Groups and Diseases", Prof. S.C. Tiwari highlighted the reported associations between blood groups and diseases of the gastrointestinal tract, malignancies of the reproductive system and other organs. Prof. Tiwari discussed the importance of the endemic infectious diseases in maintaining the gene frequencies of ABO blood groups in different geographical regions of India.

Introducing the concept of Histocompatibility and Human Lymphocyte Antigens, Dr. N.K. Mehra explored the possible utility of HLA and disease associations as diagnostic tools in case of endemic diseases in the country.

Reviewing the present state of knowledge on inbreeding in India, Dr. S.K. Basu pointed out the lacunae in methodology of such studies and stressed the need for exploring consanguinity data with new approaches in evaluation of their effects on health status.

Prof. I.P. Singh dwelt on "Medicogenetic Problems among the Tribal Communities in India". Reviewing their needs and the existing bottlenecks, Prof. Singh, sought the effective coordination between the various agencies and development programmes in alleviating the sufferings of the tribal groups.

Shri P. Padmanabha in his keynote address "Population Trends among the Tribal Groups", critically reviewed the various demographic correlates and analysed the growth rate projections among the tribals from census data. Shri Padmanabha touched upon the various issues concerning the development of the tribal population groups within their socio-cultural set-up.

Dr. S.S. Agarwal, speaking on the "Concept of Genetic Counselling and its Scope in the Indian Context", listed the essentials of genetic counselling and emphasised upon the importance of genetic counselling as a component of health care.

In the same session, Dr. L.M. Ambani, while talking on his experiences on deriving the empirical risk estimates in the mentally retarded children, brought forth salient features of practical significance in the organisation of effective genetic counselling services.

Delivering the valedictory address, Col. B.L. Raina* felt that the subject Population Genetics and Health Care was within the framework of Alma Ata Declaration 1978. Col. Raina pointed out that our concern on Population and Family Planning implied that children should be free from diseases and disorders arising out of genetic and genetico-environmental factors. He said a comprehensive knowledge on the genetic diseases could be achieved by adopting a multidisciplinary and collaborative approach and equipping the centres engaged in population genetic studies with properly trained personnel and facilities.

*Formerly, Director of Family Planning, Government of India, Director, National Institute of Family Planning and United Nations Population Advisor.

Observations and Recommendations of the Workshop

Concerted programme efforts having been made to control the environmental diseases, the genetic and genetico-environmental diseases are assuming more and more importance in the Health care delivery system. The idea of holding a Workshop on Population Genetics and Health Care was conceived at the National Institute of Health and Family Welfare in order to provide a platform for constructive interactions between the Population Geneticists, Clinicians, Health Administrators and Policy planners.

Unlike the conventional Scientific meetings, the methodology of the workshop was designed in such a way that the keynote speakers provided the background information in particular areas of Population Genetics and its importance in Health Care. In the light of this information each topic was discussed thread bare in the group discussion sessions. These sessions, often volatile, threw up interesting ideas. The proceedings of these sessions were recorded. On the basis of these discussions, observations and recommendations of the workshop on the various areas of Population Genetics having relevance to the health and family welfare were framed. These were presented in the concluding session for adoption. A unique feature of this workshop was that attempts have been made to put out the observations and recommendations in a form that may be useful to the health administrators and policy planners as well as guide the research workers towards more meaningful and fruitful endeavours.

HAEMOGLOBINOPATHIES AND ALLIED DISORDERS IN INDIA GENETIC IMPLICATIONS AND IMPORTANCE IN HEALTH CARE

Observations

1 Studies so far carried out on abnormal haemoglobins and incidence of G-6-PD deficiency in various population groups show variations in haemoglobin pattern and also quantitative variations in G-6-PD activity. However, attempts so far made to correlate these abnormal markers with clinical profiles and its variations are meagre.

2 A genetic disorder is often found to be associated with other clinical conditions e.g. Down's syndrome having a high association with thyroid diseases.

3 Discrepencies noted in the qualitative and quantitative data on these genetic markers from different centres can be attributed to want of uniform methodology in such studies.

4 An association may exist between haemoglobinopathies and G-6-PD deficiency.

5 The studies available on abnormal haemoglobins and G-6-PD deficiency are confined to certain geographical areas and to limited population groups.

6 Multicentered, collaborative studies on haemoglobinopathies and G-6-PD deficiency will be more useful.

7 In the treatment of thalassaemia and related disorders, effective line of therapy and paucity of adequate medicines were highlighted.

8 Prevention of genetic disorders due to thalassaemia and related disorders is desirable.

Recommendations

1 Studies on clinical profile and variations in detail, of the various abnormal haemoglobins, thalassaemia and G-6-PD deficiency should be undertaken.

2 Proper study of correlative factors in the high risk group would be of importance to health care.

3 The investigations on haemoglobinopathies and G-6-PD deficiency should adopt a uniform methodology for proper evaluation and comparison of the results from various centres.

4 Same blood sample should be investigated for G-6-PD deficiency, thalassaemia, Hb S and other abnormal haemoglobins for effective application in health care. Simultaneously, studies on drug sensitivity in G-6-PD deficient subjects should be undertaken.

5 The studies on haemoglobinopathies and G-6-PD deficiency should be extended to the unexplored regions and population groups with emphasis on scheduled castes and scheduled tribes following multi-disciplinary and multi centered approach for effective application in health care.

6 In case of homozygotes for Hb S, Hb E and interaction of such traits with thalassaemia, clinical profile should be studied and stress laid on therapy including prompt treatment of infection and folic acid deficiency, blood transfusion and administration of chelating agents.

7 The efforts of centres already engaged in researches on haemoglobinopathies and G-6-PD deficiency should be brought together. A workshop may be organised to develop uniform protocols and methodology which may be adopted by the workers in the field.

8 Due consideration should be given to the cultural attitudes of the people concerned towards health and disease in policy making.

9 Studies on the prenatal diagnosis of haemoglobinopathies and G-6-PD deficiency should be undertaken.

10 Effective line of therapy for various abnormal haemoglobins and thalassaemia syndromes should be outlined. In this context, liberalisation of import of chelating agents, which are not manufactured in India, is strongly recommended.

ASSOCIATION OF GENETIC MARKERS WITH HEALTH AND DISEASES

Observations

1 Significant associations have been observed between ABO blood groups and ABH substances with several diseases, for example, malignancies of the gastrointestinal and reproductive tract and some other diseases such as gastric ulcers etc.

2 Information on the association of other blood group markers and diseases is lacking with reference to Indian populations, although significant associations between, Duffy factor (Fy^{a-}, Fy^{b-}) and malaria, loss of ABH antigens in haematological malignancies such as leukemia have been reported in studies carried out in other parts of the world.

3 Strong associations have been reported between HLA antigens and diseases like ankylosing spondylitis, rheumatoid arthritis, insulin dependant diabetes mellitus etc. Information on the relationship between HLA antigens with tropical diseases is scanty. Very few centres in India are engaged in HLA studies although there is a lot of scope for such studies, particularly in relation to the prevalent diseases in our country.

4 Association between diseases and several other genetic markers such as red cell enzymes, serum proteins etc. have not been investigated in detail.

Recommendations

1 There is a need to study in detail with proper control the relationship between various genetic markers and diseases, particularly those which are endemic in India and also the malignancies.

2 It is important to investigate association between malaria and Duffy and other blood types in view of widespread prevalence of malaria in the country.

3 In view of the extensive polymorphism of the HLA system, the association of these antigens with various diseases prevalent in the country such as infectious diseases, auto-immune disorders etc. should be investigated, with emphasis on family studies as far as possible.

4 The studies on association between genetic markers and diseases should incorparate as many genetic markers for sharper delineation of the high risk group.

5 Where strong associations between blood groups and diseases have been established, the underlying pathophysiological and biochemical mechanism should be studied. The existing knowledge of significant association between genetic markers and various diseases should be applied to identify the high risk indivlduals/population which can provide the basis for augmenting preventive and promotive aspects of health care.

INBREEDING IN INDIA, ITS GENETIC CONSEQUENCES AND IMPLICATIONS IN HEALTH CARE

Observations

1 India provides an excellent opportunity for the study of inbreeding and consanguinity. Review of the literature suggests that while the nature and extent of inbreeding among several communities has already been documented, vast areas of the country are yet to be explored. On the whole, the practice of consanguinity is more common in the southern region of the country.

2 Numerous investigations have been undertaken in the country and abroad to understand the effect of consanguinity on the frequency of genetic disorders, rates of fertility, mortality and morbidity and physical growth and development patterns. However, the results obtained from these studies are often contradictory.

3 Also the inbred populations provide an excellent opportunity to discover genetic disorders (recessive traits) and their variations.

4 Variations in the development of inbreeding practices and their history in different communities are evident from available studies.

Recommendations

1 There is an urgent need to undertake in depth investigations on inbreeding and its effects in communities and areas not covered so far.

2 It is desirable that in future studies standard genealogy approach should be followed and wherever possible, the inbreeding co-efficient should be established through other measures such as phenotypic and genotypic bioassays.

3 As far as possible the future investigations on the effect of inbreeding should be carried out with a multidisciplinary approach and emphasis should be laid on the following :

(a) Sampling.

(b) Proper control.

(c) Emphasis should be laid on prospective rather than retrospective studies.

(d) Variables such as fertility, mortality, morbidity rates, genetic disorders, congenital malformations, physical growth and development should be carefully studied, keeping in view the socio-economic and other environmental variables.

4 The biological effects of inbreeding and parental consanguinity must be viewed in terms of the antiquity and extent of inbreeding in a given population.

5 Informations collected from the studies on inbred populations may be used for assessing the risk figures for these populations.

6 To create public awareness about the effect of inbreeding and consanguinity, suitable mass media should be utilised. Guidelines depending upon the given situation should be suitably evolved.

GENETICO-ENVIRONMENTAL STUDIES ON INDIAN TRIBES CONSIDERATION OF APPROACHES FOR PROMOTION OF HEALTH CARE

Observations

1 The frequency of different genetic and other disorders among the tribal populations are yet to be documented.

2 Serious efforts have yet not been made to understand the expressivity of the genetic disorders in different environmental conditions, for example, parasitic load, nutritional status, changed habitat and climatic conditions.

3 Data on demographic correlates such as fertility, mortality and morbidity rates are rather scanty.

4 Reasonably detailed data on the incidence of some of the genetic disorders like Hb S and G-6-PD deficiency are available for several tribal populations.

5 Efforts so far made to understand the nature and extent of use of indigenous medicines as well as health practices are not equal to the need.

Recommendations

1 Extensive systematic investigations are needed to estimate the frequency of genetic and other disorders and their physical, social and environmental correlates and their interactions. This information will form the basis of identification of high risk tribal groups.

2 Urgent studies are required specially for small size tribal populations living in an inhospitable environment threatened by the prospect of demographic extinction as measured by fertility, mortality, morbidity and migration etc. and determinants thereof.

3 In the tribal groups showing high incidence of genetic disorders like Hb S, G-6-PD deficiency and thalassaemia, the clinical profile of the carriers as compared to

the normal individuals/populations should be urgently studied to determine the extent of health hazards.

4 Information on the indigenous medicine and health practices should be obtained through multidisciplinary studies.

5 There is an urgent need to evaluate the nutritional values of the traditional foods as well as changing patterns of dependence on traditional food and dietary practices.

6 Tribal research institutes should be strengthened to undertake multidisciplinary, collaborative studies specially in the area of nutrition and health. These institutes should make efforts to establish base laboratories in the tribal areas.

7 The number of primary health centres in the tribal areas should be further increased. Efforts should be made to strengthen the existing machinaries such as ICDS blocks as well as tribal development blocks, for providing medical care to the tribal population.

GENETIC COUNSELLING

Observations

1 (a) Genetic factors are important causes of several types of medical problems such as, mental retardation, congenital malformations, infertility and recurrent early abortions etc.

(b) Scientifically, the need for genetic counselling in Indian context is no different than that of the advanced countries of the world.

(c) Even in terms of priorities its importance cannot be ignored. India is a large country and even rare disorders are numerically important. Moreover, human suffering cannot be quantified only in terms of numbers.

2 The response of the Indian people to genetic counselling has been very encouraging and positive where such facilities have been made available.

3 Accurate diagnosis, an important element in the genetic counselling process, requires well trained staff and adequately equipped laboratories.

4 Genetic counselling needs to be viewed in the larger context of overall management of genetic disorders, including antental diagnosis, neonatal screening and treatment of affected individuals. This shall also include educational and psychological support to the family.

5 There are hardly any data available on risks of recurrence of polygenic or multifactorial traits in Indian populations.

6 Very few centres in the country have capabilities of undertaking the responsibility of genetic counselling.

Recommendations

1 Training

(a) Refresher courses on human genetics/medical genetics should be organised for interested basic scientists, medical personnel (paediatricians,

obstetricians, etc.) and paramedical personnel (technicians, nurses, social workers etc.) to promote the awareness of the magnitude and possibilities of managament of genetic disorders.

(b) Indepth special training courses should be organised for medical and paramedical personnel and scientists who intend to take medical/human genetics speciality as a career.

2 Genetic Epidemiology

There is an urgent need to :

(a) ascertain the magnitude and burden of genetic disorders, including malformations, traits and diseases in hospital patients ;

(b) magnitude and burden of genetic disorders and malformations in different groups of general population ;

(c) standardized collection of family data on polygenic/multifactorial disorders to estimate the empiric risk of recurrence ; and

(d) the maternal and paternal age effects on incidence af chromosomal and congenital malformations.

3 Establishment of Regional Centres for Genetic Counselling

(a) Regional centres which can undertake the diagnosis, treatment and counselling of genetic disorders should be estabished. They should be equipped with properly trained personnel, facilities and resources to discharge effective genetic counselling services. For this purpose, facilities available at different institutions/universities within a region may be pooled together.

(b) More emphasis should be given on genetic education at community level among high risk populations.

(c) Studies on screening of newborns for inborn errors of metabolism e.g. congenital hypothyroidism, PKU, etc., should be undertakan for application to population at large.

(d) Studies on antenatal screening of high risk pregnancies, such as open neural tube defects, Down's syndrome, advanced maternal age etc. should be carried out.

4 Attempt should be made to organise a central registry to document genetic disorders in India.

5 Central data bank and clearing house to review the Indian literature for dissemination of information in the field of human genetics should be established. It can also help in co-ordination of the clinical and research activities of the different centres in the country.

PRIORITY AREAS AND CENTRES FOR COLLABORATIVE RESEARCH IN HUMAN POPULATION GENETICS FOR THE PROMOTION OF HEALTH CARE

Observations

During the deliberations it emerged clearly that the frequency of various genetic disorders e.g. Hb S, thalassaemia, and G-6-PD deficiency is quite high in some of the tribal and non-tribal population groups. Consensus prevailed that in many of these studies attention has not been paid to nutrition, socio-cultural, socio-economic, inbreeding and environmental variables which might influence the manifestation of the diseases. It was agreed upon that the prevalence of various parasitic and infectious diseases in different parts of the country contribute differently to the mortality and morbidity in the population groups.

In view of the prevalence of various infectious diseases in the country, it was observed that there is a need to understand the association of different infectious diseases with genetic markers. It was further pointed out that such studies will help to delineate the high risk groups for promulgation of better health care.

It was also pointed out that the available information on consanguinity and inbreeding related to a very few population groups. Studies on effects of inbreeding on fertility, mortality and morbidity on selected few populatian groups have produced contradictory results. Adequate attention has not been paid to smaller population groups (tribal/non-tribal) despite their dwindling numbers.

Deliberations were held on the feasibility and utility of goal oriented, multi-centered, multidisciplinary and timebound approach in studies on various aspects of human population genetics.

Recommendations

1 Investigations on populations having high incidence of Hb S, thalassaemia and G-6-PD deficiency should be undertaken.

2 Multidisciplinary studies on the effects of consanguinity on fertility, mortality, morbidity rates, genetic disorders, congenital malformations and physical growth and development should be undertaken with due consideration of the socio-economic and environmental variables following a standard genealogy approach.

3 Investigations on the association of genetic markers with diseases using as many genetic markers as possible and multivariate analysis approach should be initiated for sharper delineation of susceptibility/predisposition/and high risk groups.

4 Indepth, multidisciplinary, multicentered studies on small sized populations (tribal, non-tribal, isolates etc.) must be initiated.

Approaches

1 Investigations should be multidisciplinary and multicentered.

2 Standardised techniques, uniform methodology including proper control should be adopted.

3 Investigations should incorporate many genetic markers and the study design should take into account the socio-economic and environmental variables.

4 Wherever possible, genetic epidemiological studies should be conducted for both genetic disorders and other diseases.

Evolved Strategies

1 A directory of various institutions in different parts of the country engaged in Population Genetic Studies should be prepared, preferably by National Institute of Health and Family Welfare, New Delhi.

2 It was agreed that in order to ensure effective implementation of the above recommendations, a central coordinating body may be constituted to evolve suitable strategies for exchange of technical knowhow by organising workshops, training programmes and study groups etc. In view of the efforts already made by National Institute of Health & Family Welfare in this direction, it was unanimously agreed that this responsibility should be borne by National Institute of Health and Family Welfare.

SESSION I

Haemoglobinopathies and Allied Disorders in India : Genetic Implications and Importance in Health Care

Keynote Addresses :

Abnormal Haemoglobins in India—A Critical Appraisal with Particular Reference to Promotion of Health P. K. SUKUMARAN

Glucose-6-Phosphate Dehydrogenase Enzyme Deficiency in India : Prevelence and Public Health Implications ARVIND J. BAXI

Highlights of Discussions

Abnormal Haemoglobins in India - A Critical Appraisal with Particular Reference to Promotion of Health

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Human haemoglobin is heterogeneous at all phases of development. In normal adults the major component, comprising about 97 percent of the total haemoglobin, is haemoglobin A. A minor component haemoglobin A_2 accounts for 2.5 percent and haemoglobin F, the main haemoglobin in foetal life, is about 0.5. percent. The normal haemoglobin has tetrameric structure consisting of two pairs of unlike polypeptide chains and to each chain is attached one haem molecule. Thus adult and foetal haemoglobins have α-chains associated with β (Hb A, $\alpha_2\beta_2$), (Hb A_2, $\alpha_2\,\delta_2$) or γ-chains (Hb F, $\alpha_2\gamma_2$). Three or perhaps four different forms may be found to occur in intrauterine life. They are haemoglobin Gower 1 ($\zeta_2\varepsilon_2$); haemoglobin Portland ($\zeta_2\gamma_2$); haemoglobin Gower 2 ($\alpha_2\varepsilon_2$) besides haemoglobin F. The zeta (ζ) and epsilon (ε) chains are the embryonic counterparts of the α and β, γ or δ chains respectively. Similarly there are two different molecular species of Hb F in which the γ-chains have either glycine ($G\gamma$) or alanine ($A\gamma$) at 136 position. There is evidence to show that α-chains are also duplicated. It is now known that genes for synthesis of α-chains and their embryonic counter part (zeta-chain ζ) are located on chromssome 16 and the genes for the synthesis of γ, β, δ and epsilon chains (ε) are on chromosome 11.

Abnormal haemoglobins are haemoglobin variants resulting from genetically determined abnormal synthesis of globin part of the haemoglobin molecule. The abnormalities can be in the structure or in the rate of synthesis of the polypeptide chains. In the former, a single base change (one of the triplet nucleotides or codons) in the DNA structural gene leads to the insertion of an incorrect amino acid in the protein and may cause disease. Examples of these are : Hb S, C, D, E, G, Q, Norfolk

etc. In the latter, there are no electrophoretically detectable haemoglobin variants, but there exists evidence for reduced synthesis of one or the other polypetide chains. Thalassaemias belong to this group of variants (β°, β^{+}, α, $\delta\beta$-thalassaemia etc.). There is a gradual decline in the amount of foetal haemoglobin (Hb F) present after birth. Hereditary persistence of foetal haemoglobin (HPFH) is a condition characterised by the persistence of foetal haemoglobin into adult life in the absence of any marked haematological abnormalties.

Abnormal Haemoglobins

Although more than 300 different abnormal haemoglobins are so far reported, only a few of them are of clinical importance. They include haemoglobins S, C, D, E either in homozygous state or in combination with one another or in combination with thalassaemia. Thalassaemias (β, α, δ) and their variants also belong to this group.

In recent years incidence of haemoglobinopathies have been reported from different parts of India. As childhood diseases due to malnutrition and parasitic infestations are on the decline due to better medical care, genetic diseases seem to emerge to the forefront. Haemoglobinopathies, must therefore, become an increasingly important group of diseases, atleast in certain ethnic groups in this country. The different abnormal haemoglobins seen in this country are enumerated below, along with some of their characteristic findings.

Haemoglobin S : This is a beta chain variant with substitution of valine for glutamic acid at 6 position. This is the most widespread haemoglobin variant in India. This was first reported from Nilgiris, South India, among the tribal groups and tea garden workers in Assam (Lehmann and Cutbush, 1952 ; Dunlop and Mazumdar, 1952). Sickle cell trait in the various tribal groups in South India ranges from 4-40 percent Some scheduled castes in Andhra Pradesh showed high incidence (more than 28 percent). Limited studies have revealed cases of sickle cell thalassaemia and sickle cell anaemia in some of them.

In Western India and Central India this gene was found ranging from 4 to 22 percent in some tribal groups, while some tribes in Gujarat showed ranges varying from 3 to 33 per cent. Sickle cell anaemia and sickle cell thalassaemia were recorded from some scheduled caste cases in Gujarat and some migrated groups from that region in Maharashtra. Incidence of sickle cell trait as high as 20 per cent has been reported from Mahars of Maharashtra along with incidence of sickle cell disease. Bastar is a region from where sickle cell trait of varying frequencies are documented. Oriyas of Orissa and Bhils of Rajasthan are reported to have this

gene in high frequencies. (Sukumaran 1975, Kate et al. 1975, Goud 1977. Swarup-Mitra 1978). Thus, haemoglobin S is widely distributed in different parts of India, although disease manifestations due to this gene (sickle cell anaemia or sickle cell thalassaemia) are known in only a few of them. This is partly due to lack of studies on the disease pattern in these groups.

Haemoglobin E : This is also a beta chain variant with glutamic acid at 26 position replaced by lysine. This gene is found in high frequencies in North-Eastern region. It has been reported that in some population groups in Upper Assam this haemoglobin is seen in more than 50 per cent of the people. Besides Bengal, this variant has also been found in neighbouring areas of Bihar and Orissa. Findings of haemoglobin E in combination with thalassaemia have also been reported from other parts of India, indicating that this gene is not confined to North-Eastern region.

Haemoglobin D : Haemoglobin D with an amino acid substitution, glutamic acid to glutamine at 121 position on the beta chain, known in literature as Hb D Punjab or Los Angeles is found in low frequency of about 1-2.5 percent in different parts of the country, but mainly in Punjab and Western India. This variant along with beta-thalassaemia has been reported from many ethnic groups, including South India.

Haemoglobin J : Haemoglobin J exists in India both as alpha chain and beta chain variants. In the former the mutation is at position 120, alanine substituted by glutamic acid, while in the latter it is at position 126 valine to glutamic acid. The alpha variant is known as haemoglobin Birmingham because of its similarity and the beta variant is similar to haemoglobin Hofu. Haemoglobin J is seen in low frequencies in Punjab and Western India, specially in Gujarat. Stray cases of HbJ with thalassaemia and other haemoglobin variants are also reported.

Haemoglobin K-reported in Indians is mainly from those living in Singapore, originating from South India. Cases of this variant have been documented from Goa and Madras.

Haemoglobin L, an alpha chain variant is mostly seen in Lohanas (both Gujarati speaking and Sindhi speaking groups) from Western India. It is seen in Punjab as well.

Haemoglobin M, similar to Boston type with mutation at 58 position on the alpha chain was seen in Bombay. Cases of haemoglobin M have been reported from Punjab and Bengal as well.

Haemoglobin Q seen in this country mainly among Sindhi speaking population was a new variant, not reported till then, and known as C India, showed at 64 position

histidine instead af aspartic acid on the alpha chain. In almost all cases this variant was found to be associated with beta thalassaemia.

Haemoglobin Norfolk, an alpha-chain variant with mutation at 57 position, glycine replaced by aspartic acid, has been reported among Nepali Gurkhas.

Haemoglobin Lepore, has so far been reported in one family hailing from North Canara. This is an example of fusion type of variant.

Haemoglobin koya Dora, is with an elongated alpha chain, an example of termination mutant codon for serine. This was reported in 10 per cent of the Koya Doras of Andhra Pradesh.

Haemoglobin Rampa, an alpha chain mutant at position 95, serine replacing proline, was seen in both Koya Dora and Konda Reddis in Andhra Pradesh.

Homozygous states for haemoglobin other than HbS such as Haemoglobins D and E are almost symptomless or with mild degree of anaemia. The double heterozygote disorders show variable clinical manifestations. Hb S-thalassaemia and Hb E-thalassaemia are sometimes seen as severe as homozygous beta-thalassaemia whie Hb D thalassaemia, Hb J thalassaemia and Hb Q thalassaemia are mostly symptomless.

Thalassaemia

Thalassaemias seen in India are mostly beta type and their variants interacting with other abnormal haemoglobins. Haemoglobin H disease is the only type of alpha-thalassaemia encountered here. Most of the beta thalassaemia seen in this country answer the description of beta thalassaemia (β^0 thalassaemia) considering the clinical severity, onset of the disease, haematological and other parameters. First case of Cooley's anaemia (Mediterranean anaemia) was reported in a Bengali child (Mukherji, 1938). Later, many cases were reported from different parts of this country in various ethnic groups. Unlike haemoglobin variants, there is no abnormal haemoglobin attributable to this disease. Only indirect methods are being used for the evidence of defective synthesis of the polypeptides involved. Data available for the carriers of this gene in different population groups are limited. Levels of haemoglobin A_2 is a useful parameter for the detection of carrier state. Chain synthesis study using radioisotopes is the direct method for detecting the presence of this gene. Beta$^+$ (β^+) thalassaemia is clinically less severe, onset is delayed and requirement of blood transfusion is very less. As mentioned earlier, interaction between other haemoglobin variants and this gene do show varied severity of anaemia.

Alpha chain being duplicated, haemoglobin H disease represents alpha thalassaemia with only one functional alpha chain gene. In other words, this disease arises from existence of alpha thalassaemia 1 and 2, two alpha chain gene deleted in α thal-1 type and one gene deleted in α thal-2 type. It has been proposed that α^0 thalassaemia should represent total absence of alpha chain synthesis, α^+ thalassaemia to indicate reduced synthesis of this chain. Haemoglobin H exists as an unstable haemoglobin consisting of entirely beta chain in a tetramerric form (β_4). Unlike beta thalassaemia, it is difficult to detect alpha thalassaemia carrier state in populations unless one studies the new born babies or cord bloods. Evidence for the presence of alpha thalassaemia gene can be seen with the finding of Hb Bart's on electrophoresis. This again is an unstable haemoglobin with gamma chain in tetrameric form (γ_4).

Isolated cases of haemoglobin H disease have been reported from Bengal, Western India, Madhya Pradesh and Punjab. Results on cord blood studies done on a limited scale, have shown the presence of alpha 1-thalassaemia (Hb Bart's more than 4 per cent) and alpha 2-thalassaemia (Hb Bart's, 1-2 percent) in Bombay and Bengal.

Available data on beta thalassaemia trait indicate distribution of this gene all over the country (Chatterjee 1959, Saha and Banerjee 1973, Basu 1978, Sukumaran, 1978). In some population groups the frequency of trait appears to be very high, as much as 12-15 per cent. Homozygous beta thalassaemia found are of severe type in these groups, with affected children requiring repeated blood transfusions.

Hereditary persistence of foetal haemoglobin (HPFH) and delta/beta thalassaemia, seen in this country, are a group of haemoglobinopathies showing high level of foetal haemoglobin. They are mostly reported from Western India, though a few cases have been documented from Bengal and other areas.

Haemoglobinopathies and Community Health

Although a number of haemoglobin variants are seen in this country, only a few of them (Hb S either in homozygous state or in association with beta thalassaemia, HbE with thalassaemia or thalassaemia homozygous or its variants) are of clinical importance. As Hb S frequency is high mostly in the tribes and scheduled castes, constituting approximately one fifth of the total population of this country, attention needs to be paid to identify the different groups in them with high incidence of these deleterious genes. Cases with these genetic disorders have high morbidity rate ; intercurrent infections are rather common and most of them terminate fatally in childhood. Those who survive sometimes become crippled for life especially in sickle cell disease, with multiple infarcts after severe crises, and thus a burden to the family. Prognosis of the disease depends greatly on the environment of the patient. Those with better

standard of nutrition and living conditions progress well with prompt attention, whenever there is infection and thus avert hazardous crisis.

Haemoglobin E homozygotes enjoy reasonable health unlike sickle cell homozygotes, while Hb E-thalassaemia cases suffer from moderately severe clinical disability.

In a recent study on a small tribal group in South India, cases of sickle cell anaemia in adults with minimum clinical manifestations of the disease were noticed (Brittenham *et al*, 1977). Presence of increased levels of Hb F in them was another important finding. There was also indirect evidence for the presence of alpha thalassaemia playing a role in the clinical severity of the disease. It is known among the Arabs in the Middle East, the presence of increased levels of Hb F and or co-existance of alpha thalassaemia had an ameliorating effect on the sickle cell disease. Many sickle cell disease (homozygotes) have children as well.

Beta thalassaemia in India is an infantile disease and the affected children succumb to the disease before the age of five years unless kept alive on repeated blood transfusions. This poses tremendous economical, social and psychological problems in the family. The severe type represents β° thalassaemia and much less severe type represents β^{+} thalassaemia, are also seen in some cases.

The prevention of common genetic diseases like sickle cell anaemia, sickle cell thalassaemia and thalassaemia major, can be resorted to either by population screening and genetic counselling to discourage reproduction in proven carriers. Alternatively there may be a programme of screening by antental diagnosis for women at risk of having affected foetuses and use of therapeutic abortion in appropriate cases. Practical difficulties exist in resorting to above suggestion in our situation in different areas, where superstition, social customs play an important role. Problems in dealing with socially less priviledged groups are obvious. The social cost of a large scale programme may be seen in the context of particular medical problems of the population in such areas and groups where infant mortality is still high and other common problems such as infection and malnutrition are more pressing. It is worthwhile to ponder whether developing a genetic programme is an immediate necessity. A programme of this type has to be administered in the most tactful manner, backed by an extensive population education programme.

The programme must incorporate the help of a properly trained genetic counsellor who is able to deal with various psychological, educational and informational complexities of genetic counselling in an intelligent and humane way. It is to be borne in mind that an ill-conceived screening programme can end up in a major political, communal or social crisis.

Probably the best compromise is to set up a series of centres in high incidence areas where individuals can receive appropriate blood tests and genetic advice. This approach should be augumented with minimum necessary laboratoty facilities but not at the cost of accuracy. Studies on abnormal haemoglobins (Hb A_2 ; Hb F ; blood picture ; PCV ; sickling test etc.) and cord bloods should be taken up with priority to determine Hb Bart's for presence of alpha thalassaemia in the population groups. Medical, paramedical staff with full support of social workers, form the backbone of such studies.

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Glucose-6-Phosphate Dehydrogenase Enzyme Deficiency in India - Prevalence and Public Health Implications

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The history of the discovery of the deficiency of Glucose-6-Phosphate Dehydrogenase (G-6-PD) in human erythrocytes is well documented (Beutler, 1972, Baxi, 1972). It was observed during 1920's and 1930's that when antimalarial drugs were administered to some Negro subjects, they developed moderate to severe hemolytic anaemia. A systematic investigation into the mechanism of hemolysis by Alvin and co-workers (for details see Beutler 1972) led to the discovery of an intracellular defect of deficiency of enzyme Glucose-6-Phosphate Dehydrogenase. Further biochemical investigations revealed that deficient subjects had a highly unstable reduced glutathione (GSH) system which is responsible for protection of erythrocytes against oxidative insults (e.g. due to drugs, chemicals etc.). Lack of generation of reduced equivalents in the form of NADPH as a result of G-6-PD deficiency severely effects the ability of deficient red cells to counter the oxidative damage. Under these circumstances, the hemolysis occurs.

The G-6-PD deficiency disorder has been found to be under genetic control and the gene responsible for it is located on X-chromosome. Thus the males being hemizygous (with only one X chromosome) suffer from the homolytic episodes while the heterozygous females are rarely affected under these conditions.

Not all G-6-PD variants that are found result in severe clinical hemolysis (Beutler & Yoshida, 1973). In fact, some persons with G-6-PD variants, rarely show any sign of hemolysis. The detailed molecular biological studies show that like abnormal haemoglobins (e.g. HS, C, E etc.) many of these enzyme variants occur as a result of point mutation in the structural gene, usually through amino acid substitutions.

Geographical Distribution

It is estimated that more than 150 million people are affected by the G-6-PD deficiency all over the world (WHO 1967, Baxi 1974, Baxi 1981). In groups of people with mediterranean variant or caucasoid B-variant, people suffer from severe attack of hemolysis either on exposure to drugs, ingestion of fava beans (a staple food for mediterranean people) or sometimes in the absence of any noticeable agent. In Indian populations, the average incidence of G-6-PD deficiency is between 1-5 percent. In some population groups from North and North-West the incidence is much higher (10-18 percent). Besides that G-6-PD deficient newborns in some groups develop hemolytic disease of the newborn (HDNB) akin to that found in Greece and Italy.

Clinical and Haematological Observations

The degree of hemolysis in G-6-PD deficient patients following drug administration has been shown to depend on the type of drug, dosage etc. Though the effects of many drugs are shown to be predominantly oxidative, the direct interaction of drugs with the red cell membrane has been recently demonstrated (Baxi et al. 1978). Haemoglobinuria and jaundice are usually seen in drug-induced hemolytic anaemia. The symptoms subside on withdrawal of the offending drug. The drugs commonly used and known to produce hemolytic anaemia are shown in the Table 1.

In Indian population groups the association between G-6-PD deficiency and neontal jaundice has been well established (Baxi 1964, Deshmukh & Sharma 1968, DeCosta et al, 1969). In a large series investigated at Nowrosjee Wadia Maternity Hospital, Bombay, we have demonstrated 17 cases of G-6-PD deficient neonates among 1800 jaundiced newborns (Kothari et al. 1974). Severe hemolysis, jaundice and subsequent kernicterus have been noted in the G-6-PD deficient new borns. Thus, there is another facet of chronic hemolysis in G-6-PD deficient neonates which is qualitatively different from drug induced hemolysis.

The abnormal hematologic picture during the hemolytic phase mainly consists of anisocytosis, polychromatophilia and basophilic stippling. Spherocytosis and occasional red cell fragmentation is often evident. Erythrocytes may show heinz bodies within 24-48 hours of drug administration. The direct antiglobulin test is usually negative (deGruchy 1975).

Since the early observations made during second and third decade of this century, many drugs have been known to produce moderate to severe hemolysis in G-6-PD deficient subjects. These include antimalarials, sulphonamides, nitrofurans, acetylsalicylic acid, sulfoxone, naphthlene etc. (Smith 1966, WHO 1967) (Table I).

TABLE 1

Drugs implicated in Causing Hemolysis in G-6-PD Deficient subjects.

1 *Anti-malarials*
- Primaquin
- Pamaquin
- Chloroquin
- Pentaquin
- Plasmoquin
- Quinacrine

2 *Sulpha Drugs*
- Sulphonamide
- Sulphonilamide
- Sulpha Pyridine
- Sulpha Isoxasole
- Salicylaxosulpha Pyridine
- Sulphamethoxy Pyridine
- Sulphacetamide

3 *Nitrofurans*
- Nitrofurantoin
- Furazolidine
- Furaltadone

4 *Antipyretic/Analgesics*
- Acetyl Salicylic Acid
- Acetanilide
- Acetophenetidin (Phenacetin)
- Antipyrin
- Para-amino Salicylic acid

5 *Others*
- Sulphoxone
- Naphthalene
- Methylene Blue
- Vitamin K
- Acetyl Phenylhydrazine
- Ascorbic Acid
- Probenacid
- Fava beans
- Benzene

G-6-PD Deficiency and Drug Interaction

Since it is not possible to conduct a prospective drug trial in G-6-PD deficient persons an 'in vitro' model to screen drugs with potential hemolytic properties has been developed (Baxi et al. 1978). It was shown that the drugs such as acetylphenyl hydrazine, menadione (Vitamin K), ascorbic acid etc. produce predominantly oxidative changes through formation of H_2O_2 resulting in methemoglobin in G-6-PD deficient red cells. On the other hand, primaquin seems to act through its action on red cell membrane resulting in increased osmotic fragility and subsequent hemolysis.

Malaria and G-6-PD Deficiency

Hyperendemicity of malaria in the country imposes significant stress on the public health resources. The treatment with antimalarials in enzyme deficient individuals will additionally entail further strain with development of hemolytic complications. Thus, it is imperative that the mass screening of G-6-PD deficiency should be undertaken

so that such sensitive individuals are detected by and large and the drug sensitivity in such persons should be evaluated. Fortunately, it has been observed that not all G-6-PD deficient persons suffer from deleterious effects of drugs. However, the freedom of adverse effects of some drugs can not be generalised to all categories of the drugs. The observation also calls for intensive research into the development of a rapid 'in vitro' model system whereby red cells from the enzyme deficient individuals can be studied for the 'sensitivity' with the drug in 'question'. More simplified extension of above studies may help in determining the adverse reaction of drug(s) in G-6-PD deficient individuals.

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Highlights of Discussions : Session I

Haemoglobinopathies and allied disorders in India : Genetic Implications and Importance in Health Care

Swarup-Mitra : It is my experience that in case of haemoglobin abnormalities, not only the spleen but liver is also affected. Patients of thalassaemia show fragility of bones and frequent fractures because of slow deposition of calcium may be seen. Persistence of jaundice and some times stones have also been seen. The clinician should attempt to cut down hemolysis in these patients. Therapy is often complicated by iron overloading.

Veerraju : I have not come across a single Koya Dora variant in Andhra Pradesh. Though a high frequency of this variant has been reported from that State.

Sukumaran : Chain mutants are usually unstable and are precipitated in hemolysate. Analysis of the fresh blood samples is necessary to detect these variants.

Veerraju : How would you suggest that the screening for alpha thalassaemia be carried out in view of high mortality in thalassaemia ?

Sukumaran : Cord Blood studies should be carried out.

Swarup-Mitra : With reference to reported high incidence of Hb Koya Dora—can it be implied that the frequency of a particular Hb variant is high only in a particular ethnic group ?

Sukumaran : To arrive at any valid conclusion, systematic investigations have to be undertaken. Similar situation of a very high incidence of Hb E in normal individuals in certain population groups in eastern India have been reported.

Das : The gene frequency of Hb E is as high as 0.499 among 'Garo' and 0.535

among the 'Rabh' tribe of Assam. In homozygous Hb E parents, the reproductive wastage was found to be very high, although no fertility decline was noticed among them. Beside that, no other clinical symptoms were seen. I would like to add that our data may suggest reproductive compensation but further information on mortality, keeping in view the environmental and other variables, would be needed before it could be fed to the programme.

Swarup-Mitra : HbE is also commonly found in Bengal. The carriers often present mild anaemia and jaundice. I have not come across associated G-6-PD deficiency or thalassaemia. Liver function tests were found to be normal.

Das : There are possibilities of presence of Hb E in association with beta thalassaemia and G-6-PD deficiency in view of high frequency of G-6-PD deficiency in some population groups of Eastern region.

Bhalla : Existing reports point out a high frequency of abnormal haemoglobins, e.g. Hb S in certain population groups. It is necessary to understand the mechanism and factors responsible for the maintenance of these abnormal genes in the populations to have a fuller comprehension of the magnitude of the problem.

Agarwal : In the larger context, the knowledge on the load of genetic diseases is important in improving the health care system and to provide intervention measures. Systematic population surveys for the incidence of genetic disorders like haemoglobinopathies are needed.

Sidhu : Dr. Baxi, can you comment on the relationship between severity of hemolytic reaction with age, occurrence of subsequent reactions and possibility of different degree of reaction in different communities ?

Baxi : Why hemolytic reaction is usually more severe in adults we cannot explain. Information on subsequent reactions is also not available.

Balaraman : Dr. Baxi, have you carried out some studies on the reactors and non-reactors to the various drugs in case of G-6-PD deficient subjects ?

Baxi : We have done so but the reults are inconclusive.

Balaraman : Malarial endemicity in India induces indiscriminate use of anti-malarial drugs which may cause hemolysis in G-6-PD deficient individuals. The variations in the hemolytic reactions in different types of malarial parasite infestations would be interesting to study.

Baxi : Experience in Western India shows that not many people react to the

anti-malarial drug. I am afraid these observations are not based on extensive studies. In India, P. Vivax is predominantly found while P. Falciparum is found in different belts and regions of the country. Further studies are required in this direction.

Verma : WHO Task Force on Genetics in 1980 declared that G-6-PD enzyme deficiency and haemoglobinopathies are priority problems in different parts of the world. In view of the reported high frequency of abnormal haemoglobin and G-6-PD enzyme deficiency in some population groups of India, it is important to find out a suitable screening method. Because of diverse nutritional patterns in India, the investigators should keep in mind the possibility of induced hemolysis by food other than Fava beans. The 'invitro' model for G-6-PD enzyme deficiency can be effectively utilised for this purpose. Conservative therapy may be used in deficient subjects. I feel more laboratories should undertake screening of populations for G-6-PD enzyme deficiency and abnormal haemoglobins. Government may consider liberalisation of import of chelating agents like 'Desferal' to encourage interventions.

Baxi : I agree with Dr. Verma that detailed studies on possible hemolytic agents in beans, etc. should be undertaken. Fava bean contains methyle dopa which appears to act through stroma of the cell membrane. The therapy in G-6-PD deficient patients can be planned by obtaining the membrane profile of the red cells especially spectrin.

Swarup-Mitra : Besides the selective advantage which G-6-PD deficient and Hb S individuals have against malaria, I think there may be some other predisposing factors responsible for the maintenance of these genes in the populations.

Baxi : Extensive detailed studies are required in this direction.

Swarup-Mitra : In large parts of the country, only case reports of various haemoglobinopathies and allied disorders like G-6-PD deficiency are available. Nevertheless, I believe that gene may be present but has not been detected.

Balaraman : Among the tribal population groups especially, a lot of intrinsic and extrinsic factors may be playing an important role in the manifestation of these disorders. Dwindling growth rate, infertility, congenital syphilis, yaws, and high infant mortality rates may be given due consideration, while studying the health hazards of haemoglobinopathies.

Swarup-Mitra : In view of the limited resources available, surveys could be initiated on the clinical cases for screening of haemoglobinopathies, for example, anaemia and all cases of malarial infections, G-6-PD deficiency etc., socio-economic and socio-biological factors should be taken into account, while estimating the health hazards of haemoglobinopathies in the high risk group.

Bhalla : We should define the high risk group. I feel the pregnant women, children, populations inhabiting high altitudes and those showing a high frequency of Hb S and G-6-PD deficiency should be called high risk group. Emphasis should be on the incidence of disease and secondly it will be important to study the relative risk of mortality and morbidity in the carriers of abnormal haemoglobins as compared to normals.

Balaraman : Haemoglobinopathies and G-6-PD deficiency are specialised investigations. Centres with properly trained manpower and facilities are required. I feel studies should be multidisciplinary in nature.

Das : A few centres are already actively engaged in such studies. These centres should be strengthened and then phasewise more centres could be opened. Collaborations between these centres and the Tribal Research Institutes, for example, may be fruitful.

Sukumaran : Manpower development is the another most important facet of the whole problem.

Balaraman : It is of utmost importance to standardise the methodology. A format may be prepared for purposes of proper comparison.

Sukumaran : Prenatal diagnosis for haemoglobinopathies could help in genetic counselling. In any case for preventive measures, I would suggest screening of populations at whatsoever level considered feasible. I feel the optimal approach will be educating the school children who will have knowledge of such diseases when they establish families.

Kalla : It would be worthwhile to create a co-ordinating body for proper co-ordination of research activities in this field.

SESSION II

Association of Genetic Markers with Diseases

Keynote Addresses :

Blood groups and their Association with Diseases S. C. TIWARI

HLA and Diseases Association : A Review N. K. MEHRA

Highlights of Discussions

Blood Groups and their Association with Diseases

S. C. TIWARI

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The discovery of the human ABO blood groups in 1900 by Landsteiner was followed by investigations for elucidating pathological significance of the blood groups. Soon after it was reported that mother-foetus incompatability was the cause of haemolytic disease of the newborn, it became apparent that natural selection is operative on blood group gene frequencies. Since various human populations are characterised by differential frequencies of the blood group genes, a pertinent question emerged regarding the origin of the differences between various papulations. These differences could be attributed to random genetic drift and founder effect stabilizing the original frequencies or natural selection operating on blood groups. However, the relative contribution of these factors remains obscure and uncertain.

The finding of Aird *et al.* (1953), that the statistical relationship exists between blood group A and Carcinoma of the stomach, was the first overwhelming evidence for the association of ABO blood groups with diseases. More recently, association of various other diseases with blood groups have been reported but the pattern of selective forces remains dubious and complex.

A good deal of controversy was evoked on Mourant's (1954) question whether the antigens of infective organisms are the primary factors responsible for the polymorphism of the ABO blood groups. Brues (1954) thought that the ABO blood group polymorphism is maintained by natural selection. It was further argued by him that there had been a considerable relaxation of selection in modern times so that the "mortality causes involved may be totally different from those which decimated the young and adolescent in prehistoric times". It seems plausible that some of the infec-

tious diseases like plague and smallpox which existed in epidemic form might have contributed a small part of the selective forces in earlier times.

A majority of the anthropologists had the traditional view that the ABO blood group gene frequencies, all over the world, maintain a fairly original proportion. However, presently these expectations appear to be somewhat uncertain. Pettenkofer etal. (1962) expressed their definite opinion that there is not only serological evidence but also the general pattern of the geographical distribution of ABO genes support the hypothesis that there exists a relationship between the world distribution of the ABO genes and the history of great epidemics. Mourant (1974) stated that "the gene frequency in many, if not most, genetic polymorphisms are the results of an equilibrium, varying with locality, between the selective effects of different diseases and other environmental stresses on the various phenotypes of any given system". It is indeed difficult today to delineate the effect of epidemics on the ABO gene frequencies. But it would not be entirely speculative to say that there may be a balanced set of selective factors which maintain the present picture of diversity of ABO gene frequencies. However, Chung and Morton (1961) proposed that the "principal mechanisms of selection which maintain the ABO polymorphism act during foetal and early postnatal stages, and that the supported association between blood groups and adult disease are at the most the second order selective effects".

Compared to ABO blood group system, very little is known about the association of diseases with other blood group systems and the disparity is mainly due to lack of data. We hope, in future more data would be available on the association of diseases with other blood group systems.

Subsequent to the first report (Aird *et al.* 1953) investigation of associations with other neoplastic diseases were undertaken. Table 1 shows 580 cases of cancer of the lip being significantly associated with group A, the relative incidence A/O and B/O being 1.20 and 0.81 respectively; cancers of the tongue, gums and check are likewise associated with group A. A pooled data on all these diseases indicate significant association with group A. Cancer of the oesophagus shows somewhat different picture since both group A and B show significant association (Table 1). For the cancer of lung the A/O ratio is still lower as (1.03). Thus, the differences from unity is far below the level of significance. The corresponding ratio of 0.96 for B/O is non-significant. It is somewhat unusual that compared to several other carcinomas of other organs, the lung cancer shows the least association with the ABO blood groups. Incidentally, the association of the disease with the smoking of tobacco, particularly in males, probably obliterates the association with blood groups.

The data on the cancer of the digestive tract are far greater than any other disease. Table 2 shows the association of ABO blood groups with cancer of stomach (part uns-

specified), colon, rectum, large intestine and intestinal tract. The association with group A is noticeable in several parts of the digestive tract The cases of stomach cancer show a small increase of ABH secretors, but the results are statistically not significant.

Cancer of the breast, cervix uteri and ovary shows a clear association with group A. The relative incidence of A/O for breast, cervix uteri and ovary being 1.07, 1.23, and 1.09 respectively (Table 3).

Table 4 shows the association of ABO blood groups with gastric and duodenal ulcers. Aird *et al.* (1953) reported that peptic ulceration was strongly associated with group O. Subsequently, Clarke *et al.* (1956) further extended this work and reported that duodenal ulcer was more strongly associated with group O as compared to gastric ulcer. For duodenal ulcer A/O and B/O relative incidence was 0.73 and 0.80 respectively which is highly significant. However, for gastric ulcer both ratios have identical value of 0.87. Sheppard (1953) and Clarke *et al.* (1956) suggest that both ABO blood group system and secretor status jointly effect the predisposition to peptic ulcer. More work is needed to show the association of ulceration with ABO blood groups and ABH secretion.

There seems to be highly significant association of diabetes mellitus with blood group A compared with O (Table 4). The combined relative incidence A/O is 1.07. It interesting that the A/O ratio is higher in males than in females. However, the data so far reported are quite heterogenous and investigations in more homogenous populations are needed. It is somewhat intriguing that a disease with such high mortality could persist in such a high frequency particularly when no therapeutic methods were known in the earlier days. Aschner and Post (1956) thought that the women manifesting hereditary tendency to diabetes were on average more fertile than normal women. Post and White (1958) reported that such women menstruate at a younger age. According to Lehman (1959) the incidence of the disease was probably not high during palaeolithic time since during hunting food-gathering stage their diet was sufficiently low in its calorie and carbohydrate content. Jenkins *et al.* (1974) reported a rather low fasting blood glucose levels in the hunting food-gathering Bushmen of Kalahari desert. This may be advantageous in the primitive conditions.

A good deal of investigations have been carried out for finding associations between blood groups and rheumatic fever and rheumatic heart diseases. In both cases, the incidence of A and B is significantly elevated. Recently, Tills *et al.* (1981) failed to demonstrate a strong association between ABO blood groups and epilepsy.

Association of several infective diseases with blood groups have been listed in Table 5. Bacterial infections like typhoid and paratyphoid do not reveal a clear picture but they do show elevated frequency of group O. Unfortunately, data on plague or cholera are not available. More recently, however, Brura and Paguio (1977) reported ABO blood group distribution among 120 cases of cholera and cholera like diarrhoea from Philippines. They found a relatively larger number of individuals of group O in both the cholera and non-cholera diarrhoeal patients. Further, group A was reported to be infrequent, whereas group B was normally distributed.

Tuberculous infection shows erratic pattern of association. A more recent study reported by Overfield and Klauber (1980) on the association of ABO groups with tuberculosis failed to show any significant association.

The association of viral infection with blood groups is of considerable interest with particular reference to smallpox, since the disease was prevalent in India in epidemic form.

Vogel and Chakravarti (1966) reported an extremely high value of A/O relative incidence (10.13) for fatal cases of smallpox. These results are not in good agreement with those of Bhattacharyya *et al.* (1965) and Sukumaran *et al.* (1966). The pooled data, however, reveal A/O relative incidence for fatal cases as 2.27. (Table 6)

Pettenkofer and Bickerich (1960) performed certain immunization experiments in rabbits to examine whether virus of smallpox contains blood group like antibodies. They reported that Vaccinia virus which is closely related to Variola virus, contains A antigen. Vogel *et al.* (1960) postulated a hypothesis that smallpox could show a more severe course and higher mortality in patients of blood group A and AB as compared to group B and O. These results were contradicted by Harris *et al.* (1962); Rondale (1963) and Harris (1963). They argued that A antigen came from the egg membrane on which the virus was grown. The assumption that the world distribution of ABO blood group genes may have been influenced by some great epidemics in the past was also considered erroneous by Springer and Weiner (1962).

Pettenkofer *et al.* (1962) however, maintained that the blood group O and B in smallpox infection has an immunological advantage compared to people with blood group A. He argued that the serum of individuals with the blood group O or B always contains anti-A and during smallpox infection the virus in reaction with the antibody anti-A is inhibited.

Vogel (1964) examined this problem in a more direct way by studying the relationship between blood groups and smallpox. He suggested that if the virus did contain A antigen, it would react during viraemia with anti A present in the blood group

B and O patients, and the disease would take a milder course. This problem was further studied by Azevedo *et al.* (1964). However, Krieger and Vicente (1969) did not find any association between smallpox and A blood group.

In the protozoal infections, malaria occupies a special place. For generations mankind has lived with malaria, or to be more exact, has lived despite malaria. It is incredible that in 1880 one half of the entire mortality of the human race was attributed to malaria. It was present in endemic form in the entire equitorial region of the world. Despite the considerable importance of the disease, it is unfortunate that very little work has been done on the association of malaria with blood group systems. The existing data show a marked excess of A in patients as compared with O and B (Table 5). Athreya and Coriell (1967) suggested that group B enjoyed a selective advantage in relation to malaria and the distribution of group B in the old world corresponded with the prevalence of malaria which was endemic in these areas. Table 5 shows the presence and absence of malaria parasite in O,A,B and AB blood groups. Miller *et al.* (1975) reported the association of Duffy blood group with malaria.

One would reasonably expect that if there was a selective effect of smallpox and malaria on the frequency of gene A, certain areas where smallpox and malaria were in epidemic form should be expected to have low frequency of gene A, more so in areas where the above infectious diseases were in endemic form for a long time.

Climatically, North India could be roughly divided into two distinct zones; the northern hilly tract extending from Kashmir to Arunachal Pradesh, including Nepal with temperate and sub-temperate climate, and the Indo-gangetic plane with sub-tropical hot and humid climate. The Indo-gangetic plane provides optimum conditions for both smallpox and malaria to be present in its virulent form. On the contrary, the Himalayan areas remained relatively free from these diseases, firstly due to climatic conditions and, secondly, due to sparse population density and the splendid isolation which they enjoyed in the not too distant past. These two factors may have significantly contributed in reducing or at least minimizing the selection pressure due to smallpox and malaria.

In one of our earlier papers (Tiwari, 1972) it was pointed out that in nearly all the population groups of Indo-gangetic plane, the frequency of group B is in excess of group A. The frequency of group A averages around 23 percent and that of B around 37 percent. According to Mourant (1976) Indian region is "characterized by relatively high frequencies of B". Immediately above this zone of high B, there runs a narrow belt of high A extending from Western Himalayas to Eastern Himalayas. In the Eastern Himalayan area, higher frequency of group A with relatively low B are found among the Angami Naga (Mitra 1936, Bhattacharjee 1939), Konyak Angami, Lhota, Rengamas and Sema Naga, Konyak (Brit. Assn. Res. Comm., 1939), Nocte Naga (Bhattacharjee,

1957), Minyong Abor, Padam Abor, Pasi Abor, Pangi Abor and Galong Abor from Abor hills (Bhattacharjee 1954), Khasi (Macfarlane 1941, Basu 1938, Das 1969), Lushai from border of Burma (Mitra 1936), Rankhal and Tipperah (Gupta 1957) from Tripura. High group A with relatively low B was also reported among the Bhotias mixed with Lepchas from Nepal, Bhutan, Sikkim and Darjeeling, Nepali inhabitants of Kalimpong (Macfarlane, 1941), Lepchas of Kalimpong (Macfarlane 1941), some population groups of Bhutan (Mourant *et al.* 1969), Gurkhas (Agar 1946), and some Newar groups of Nepal (Bhasin 1970). This high frequency of group A is maintained among the Brahmins and Rajputs of Garhwal (Tiwari and Bhasin 1968). Rajputs of Tehri Garhwal (D.U. 1953), Khasa Brahmins Khasas of Jaunsar (Majumdar and Bahadur 1952), Upper castes of Jaunsar Bawar (Banerjee and Kumar 1953), Kanet of Simla hills (D.U. 1957), Kinner Kanet of Chini Valley (Bhalla 1961), Rajputs and Brahmins of Kulu and Katra (D.U. 1958) and Rajputs of Manali (D.U. 1982) (Figure 1 and 2).

It is of particular interest to note that the various Naga tribes of Nagaland and Kanets of Simla hills and Chini Valley have no ethnic similarity whatsoever and therefore the possession of high group A compared to B is somewhat puzzling. One may argue that such resemblances are a matter of chance but the fact that it is almost uniformly present in several Himalayan populations remains unexplained.

However, if we postulate that due to high incidence of smallpox and malaria in the Indo-gangetic plains, blood group B and O were at advantage as compared to A and AB, a low frequency of group A due to selective pressure can be reasonably expected. This selective pressure seems to have been somewhat relaxed in the Himalayan area.

The wide variation in blood group frequencies in different human populations could be partly attributed to natural selection operating under different environmental conditions. These associations are of great relevance particularly when the origin of a certain disease is not properly understood. According to Mourant *et al.* (1978) "It may even, in rare cases, serve as an aid to diagnosis". The resistance and susceptibility to infectious diseases due to presence of certain blood groups is of importance to clinical medicine. It would mean that one or more diseases caused in a particular environment may have more severity in persons of a particular blood groups compared to the other. The possibility that active immunization may be effective in certain situations, is of importance. It is known that purified immunoglobulin obtained from hyperimmune adults when inoculated into young children suffering from acute malaria, fever and parasitaemia virtually disappeared. Of course, the acquisition of immunity against one specific species of malaria does not give protection against another. Thus the immunoglobulins obtained from immune persons could be used for preventing and curing the disease.

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TABLE 1

The ABO blood group system and their association with some Neoplastic diseases

Diseases		Blood group O	A	B	AB	Total	R.I A/O	$X^2_{(1)}$ for difference from unity	p	R.I B/O	$X^2_{(1)}$ for difference from unity	p
Malignant Neoplasma of :												
Lip	P	206	309	39	26	580	1.20	3.95	.05>p>.02	0.81	1.51	.25>p>.20
	C	14174	16789	4958	1570	37491						
Tongue	P	123	150	106	25	404	1.28	3.80	.10>p>.05	1.33	3.71	.10>p>.05
	C	24258	26761	12899	3971	66983						
Gum	P	18	15	29	1	63	1.12	0.10	.80>p>.75	1.26	0.57	.30>p>.25
	C	6048	4656	7992	1772	20468						
Cheek	P	99	84	139	12	334	1.62	6.11	.02>p>.01	1.49	4.52	.05>p>.02
	C	2033	1381	2303	383	6100						
Buccal cavity	P	66	72	45	17	200	1.05	0.07		1.18	0.64	
	C	12469	11714	10551	2881	37615						
Oeso-phagus	P	1070	1083	382	124	2659	1.10	4.65	.05>p>.02	1.29	16.11	p<.001
	C	182874	134480	45841	15025	432220						
Bronchus	P	3104	3627	1039	408	8183	1.07	4.53	.05>p>.02	1.04	0.77	.05>p.>.30
	C	44141	44565	11341	4474	104521						
Lung	P	3581	3279	761	283	7904	1.03	1.01	.50>p>.30	0.96	1.07	.50>p>.30
	C	167337	111975	37117	11707	328138						

P—Patient C—Control RI—Relative incidence

TABLE 2

The ABO blood group system and their association with some Neoplastic diseases of the digestive tract

Diseases		Blood group					R.I	$X^2_{(1)}$ for	p	R.I	$X^2_{(1)}$ for	p
		O	A	B	AB	Total	A/O	difference from unity		B/O	difference from unity	
Malignant Neoplasm of : Stomach (part unspecified)	P	19428	24110	6871	2746	53155	1.22	369.48	<.001	1.08	23.68	<.001
	C	1021902	968570	299119	140313	2429404						
Colon	P	679	714	187	73	1653	1.15	6.44	.02>p>.10	1.44	2.19	.20>p>.10
	C	148583	54757	19473	5664	172767						
Rectum	P	1047	1150	345	143	2685	1.07	1.87	.20>p>.10	0.98	0.11	.75>p>.70
	C	104014	60135	24859	7782	196790						
Large intestine	P	722	242	103	40	607	0.93	0.52	.50>p>.30	1.03	0.05	.90>p>.80
	C	10182	10685	7455	2344	30666						
Intestinal tract	P	455	542	163	60	1220	1.21	7.76	.01>p>.005	1.10	0.88	.80>p>.75
	C	21749	15429	5261	1632	44071						

P—Patient C—Control.

TABLE 3

The ABO blood group system and their association with Neoplastic diseases cf the Breast, Cervix uteri and Ovary

Diseases		Blood group O	A	B	AB	Total	R.I A/O	$X^2_{(1)}$ for difference from unity	p	R.I B/O	$X^2_{(1)}$ for difference from unity	p
Malignant Neoplasm of :												
Breast	P	4838	5182	1625	545	12190	1.07	11.34	<.001	1.02	0.59	.50>p>.30
	C	381911	278017	121208	37986	819122						
Cervix uteri	P	9327	9164	3520	1244	23255	1.09	28.68	<.001	1.02	0.68	.50>p>.30
	C	327118	365039	169453	70105	931715						
Ovary	P	1157	1503	373	142	3175	1.23	25.21	<.001	1.09	1.90	.20>p>.10
	C	90782	95104	25545	10435	221866						

P—Patient C—Control

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TABLE 4

The ABO blood group system and their association with Gastric/Duodenal ulcers and Diabetes Mellitus

Diseases		Blood group					R.I A/O	$X^2_{(1)}$ for difference from unity	p	R.I B/O	$X^2_{(1)}$ for difference from unity	p
		O	A	B	AB	Total						
Gastric ulcers	P	12981	11577	4172	1661	30391	0.87	107.46	<.001	0.87	49.64	<.001
	C	488365	454900	161163	61261	1165689						
Duodenal ulcer	P	17334	12767	4919	2039	37059	0.73	624.04	<.001	0.80	161.46	<.001
	C	455396	408464	147687	53964	1065511						
Diabetes Mellitus	P	9470	9717	3366	11182	23735	1.07	18.83	<.001	1.05	4.13	.05>p>.02
	C	176477	161540	53287	18414	409718						

P—Patient C—Control

TABLE 5

The ABO blood group system and their association with some Infective diseases

Diseases		Blood groups O	A	B	AB	Total	R.I A/O	$X^2_{(1)}$	p	R.I B/O	X^2( )	p
Bacterial infections												
Typhoid	P	421	315	156	64	956	0.87	3.20	.10>p>.05	0.94	0.39	.70>p>.50
	C	69938	30676	14840	4243	119697						
Viral infection												
Smallpox (survivers)	P	430	414	486	125	1455	1.27	7.94	.005>p>.001	1.10	1.43	.25>p>.20
	C	5750	3511	4839	1118	15218						
Smallpox (Fatal)	P	110	167	82	51	410	2.27	27.21	<.001	0.89	0.38	.70>p>.50
	C	3900	2599	3681	903	11083						
Protozoal infection												
Malaria	P	1050	1407	815	371	3643	1.31	19.30	<.001	1.01	0.06	.90>p>.80
	C	55569	54811	11018	4124	125522						

P—Patient C—Control

TABLE 6

ABO blood groups and incidence of Smallpox surviors and fatal cases

Smallpox	Blood groups					Authors
	O	A	B	AB	Total	
Fatal	34 (15.11)	130 (57.78)	28 (12.44)	33 (14.67)	225	Vogel and Chakravarti, 1966
Survivor	32 (15.09)	86 (40.57)	23 (34.43)	21 (9.91)	212	
Fatal	51 (43.22)	18 (15.25)	35 (29.66)	14 (11.86)	118	Bhattacharyya et al. 1965
Survivor	86 (34.13)	68 (26.98)	73 (28.97)	25 (9.92)	252	
Fatal	25 (37.31)	19 (28.36)	19 (28.36)	4 (5.97)	67	Sukumaran et al., 1966
Survivor	117 (35.03)	88 (26.35)	89 (26.65)	40 (11.98)	334	
Fatal	110 (26.83)	167 (40.73)	82 (20.00)	51 (12.44)	410	Total
Survivor	235 (29.45)	242 (30.33)	235 (29.45)	86 (10.78)	798	

Figures in parenthesis indicate percentage.

FIG. 1. DISTRIBUTION OF BLOOD GROUP 'A' IN SOME POPULATION GROUPS OF HIMALAYAS.

FIG. 2. DISTRIBUTION OF BLOOD GROUP 'B' IN SOME POPULATION GROUPS OF HIMALAYAS.

HLA and Disease Associations : A Review

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Genetic markers are important tools for the diagnosis, differentiation and characterization of diseases and for the understanding of pathogenetic mechanisms underlying their susceptibility and or resistence. In the past, the relationship between polymorphic hereditary factors and diseases has been studied with particular emphasis on the red cell antigens (Mourant *et al.* 1976). These studies provided only limited information since the increased risk of a disease state in individuals with the appropriate blood group was hardly greater than those of other blood groups. These rather restricted polymorphic variants were, therefore, not useful either for diagnosis or for prognosis. With the emergence of "Immunogenetics and Transplanation Immunology" and the necessity for a long lasting organ graft in the host being felt, interest on studies of the transplantation antigens has increased. In particular, the discovery of these antigens has led to a search for their association with diseases. These antigens are a part of the Major Histocompatibility Complex (MHC) which in man is known as the HLA (Human Leucocyte Antigens).

The detection in the HLA complex of Ir genes governing immune responsiveness to specific antigens has caused an avalanche of immunogenetic research in disease particularly those with an infectious and viral etiology. HLA, therefore, has emerged as a strong immunogenetic tool in the control of a battery of biological phenomena, including immune responsiveness and susceptibility and/or resistance to disease. Some of the important contributions of the HLA system in biology and chemical medicine have been summerized in Table I.

HLA System

The MHC in man is an extremely polymorphic system, located on chromosome

Table 1. Usefulness of HLA Testing

I. Immunological selection of properly matched donor for :

a) Solid organ transplantations, e.g. kidney, liver, heart, etc.

b) Bone marrow transplantations

c) Blood component therepy, e.g. granulocytes, platelets, etc.

II. Clinical aids in the :

a) Diagnosis and differentiation of specific diseases, e.g. ankylosing spondylitis, diabetes mellitus, etc.

b) Prediction of disease development, i.e. risk prediction for disease susceptibility.

c) Possible prognosis of certain diseases, e.g. myasthenia gravis, multiple sclerosis, etc.

d) Paternity testing for determining the exact parentage of the child.

III. Anthropological studies for determining different racial groups, the ethnicity of the population, their origin, etc.

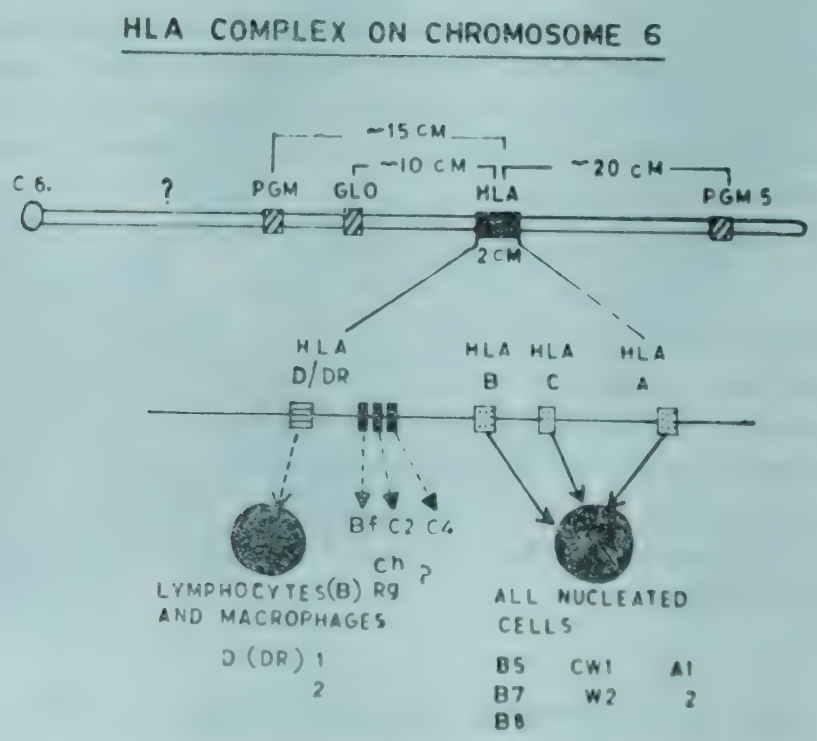

Fig. 1

number 6, presumably on its short arm. Fig. 1 illustrates some important aspects of the HLA system and its gene products. No less than seven different loci have been defined coding for at least three different types of molecules or determinants. The molecules of the first type are present on the cell membrane of almost all nucleated cells of the body and are coded for by genes situated at three loci; HLA-A,B and C. These are numbered numerically, e.g. A_1 B5, etc. and can be recognised serologically employing the complement dependant microlymphocytotoxicity test. For this reason, these three loci are popularly known as "Serologically defined" or 'SD' loci. A 'W' prefix in the number indicates that the specificity, though recognised serologically, has not yet attained the optimal definition. The second type of determinants are also membrane bound structures but have a restricted tissue distribution. These are seen preferentially on lymphocytes (mainly B lymphocytes, but also activated T lymphocytes) and macrophages, and are coded for by genes in the HLA-D locus originally. These determinants were defined by cell culture methods (Mixed Lymphocyte Culture) and are, therefore, designated as 'lymphocyte defined' or 'LD' antigens. Recently, however, serological techniques have been developed for the detection of antigens present on B lymphocytes which are identical to or closely related to the products of the HLA-D. These serologically recognised antigens in the HLA-D locus are called HLA-DR (D-Related) antigens. Finally, a third type of determinants, the serum complement factors are also coded by genes located in the HLA; the C2 and C4 of the classical and factor B (Bf) of the alternative pathway. However, it should be noted that there is still perhaps 'room' for a hundred or more, as yet undefined antigens on the seven loci.

Both type I molecules (HLA-A, +B and +C) and type II molecules (HLA-D/DR) are highly polymorphic, whereas the serum complement factors show a much lesser degree of polymorphism. About 20 different HLA-A determinants or alleles, 40 HLA-B, 8 HLA-C and 12 HLA-D/DR determinants are known and recognised by the nomenclature committee of World Health Organization (Table II). Only one allele of each locus is generally present on each chromosome and a set of combination of alleles (enbloc on the same chromosome) inherited from one parent is called a haplotype. Since every individual has a pair of chromosome 6, two antigens of each locus are generally detected in the blood, one each from the either parent. Considering the extreme degree of polymorphism that exists in the HLA system (7 linked loci with more than 90 different determinants), there are enormous number of different possible haplotypes, genotypes and phenotypes in a population (approximately 200 million different phenotypes).

HLA and Disease Associations

(*a*) *General considerations* While looking for a possible relationship between

Table II WHO Recognized HLA Specificities, 1983

HLA-A	HLA-B	8th Workshop	Prior Equivalents
	(Contd.)		
A1	BW55 (W22)	8W55	22.1
A2	BW46 (W22)	8W56	22.2 Te92. Da 30
A3	BW57 (17)	8W67	17.1 17A 17 long
A9	BW58 (17)	8W68	17.217B, 17 short
A10	BW59	8W69	HOK—1 8.2
A11	DW60 (40)	8W60	40.1
A19	BW61 (40)	8W61	40.2
AW23 (9)	BW62 (15)	8W64	15.1 TO53. 15B Te72
AW24 (9)	BW63 (15)	8W65	15.2 TO52.15A, Te71
A25 (10)			
A26 (10)	BW4		
A23	BW6		
A29			
AW30			
AW31	HLA-C		
AW32			
AW33	CW1		
AW34	CW2		
AW36	CW3		
AW43	CW4		
	CW5		
HLA-B	CW6		
	CW7	8WCW7	CVE,TOK
B5	CW8		T8.T9
B7			
B8			
B12	HLA-D		
B13			
B13			
B14	DW1		
B15	DW2		
BW16	DW3		
B17	DW4		
B18	DW5		
DW21	DW6		
DW22	DW7		
B27	DW8		
BW35	DW9		
B37	DW10		
BW38	DW11		
BW39 (W16)	DW12	DB4	DHD
B43			
BW41	HLA-DR		
BW42			
BW44 (12)	DR1		
BW45 (12)	DK1		
BW46	DR3		
BW47	DR4		
BW48	DR5		
BW49 (W21)	DR6		
BW50 (W21)	DR7		
BW51 (5)	DRW8	8WDRW8	WIAB
BW52 (5)	DRW9	8WDRW12	WIA4x7
BW53		minus 8WDRW14	
BW54 (W22)	DRW10	8WDRW14	ST—1, LTM

Table III Prominent Known HLA and Disease Associations

Nature of Disease	Antigen	Frequency		Relative
		Control	Patients	Risk
1. Rheumatic				
Ankylosing spondylitis	B27	6	93	187
Reiter's Disease	B27	6	84	85
Acute Anterior Uveitis	B27	6	51	17
2. Endocrine				
Insulin Dependent Diabetes Mellitus	B8	16	32	2.5
	B15	18	31	2.0
	BW21	4	35	12
	DR3	20	80	16
	DR4	19	49	4
Graves Disease	DR3	26	61	4.4
Addisons' Disease	DR3	26	73	8.8
Rheumatoid Arthritis	DR4	12	70	16
3. Gastro-Intestinal				
Gluten Sensitive Enteropathy	DR3	26	96	9.5
Chronic Active Hepatitis	DR3	26	71	6.8
Heamochromatosis	A3	26	73	7.4
4. Neurologic				
Myasthenia Gravis	B8	19	48	4
	BW21	4	19	5
Multiple Sclerosis	DR2	26	60	4
5. Infectious				
Leprosy	A9	—		
Tuberculoid Leprosy	DR2 DRW6	Family Data		
Pulmonary Tuberculosis	DR2 DRW6	Family Data		

HLA and a disease, two different approaches can be adopted. One of these consists of population studies in which the gene frequencies of HLA antigens in a group of unrelated patients are compared with the corresponding frequencies in a group of healthy controls. This approach gives information only on the 'association' which could either be due to direct causation (that is the associated antigen itself is responsible for the higher or lower susceptibility) or linkage disequilibrium of a disease susceptibility gene (Ds gene) with the associated HLA marker. Population studies, in general, are much easier to carry out but usually are not free from pitfalls relating to protocol design, ethnicity of the population, statistical considerations etc.

The other approach involves the family studies which allows us to see if affected relatives share HLA haplotypes more often than expected according to the general rules. Family studies have a number of advantages; (i) they allow us to detect genetic 'linkage' between the HLA locus or allele and a major disease predisposing gene and may even provide extra information on inheritence, penetration and frequency of Ds genes, (ii) there are no problems associated with population heterogeneity and (iii) those with frequent linkage disequilibria. However, in practical terms, it is more difficult to collect the appropriate families for study fulfilling all the criteria.

(b) Historical background The subject of HLA and disease associations is only a little more than a decade old. Frank Lilly (1964) first reported in inbred mice a strong association between H-2 (the MHC of the mouse) and the Gross Virus leukemogenesis. Prompted by this, Amiel in 1967 presented his findings on the association of an antigen then called '4C' (now recognized as B5, BW35, B18 and B15) in Hodgkin's lymphoma. This was followed by a large number of studies reporting significant associations in a number of diseases. The strongest associations were reported for diseases known to have a marked hereditary element and a familial clustering. Surprisingly, even those diseases with an unknown etiology and unknown mode of inheritance showed strikingly strong associations. Many review articles on HLA and disease association studies have since appeared in the literature and are quite informative (Dausset and Svejgard 1977, Bodmer 1978).

(c) Some prominent HLA and disease associations The discovery of the remarkable association between ankylosing spondylitis (AS) and HLA B-27 (nearly 95 percent frequency of B27 in AS patients compared to 8-10 percent in the controls; relative risk of approximately 192) has provided the researchers with an excellent model for studying the relationship between a disease process and an inherited antigen. Some of the prominent known HLA and disease associations are shown in Table III. Presently, attempts are being made to understand the mechanisms underlying these associations and disease predisposition.

Apart from ankylosing spondylitis, most other members of these sero-negative group of disorders viz. reiters disease, psoriatic arthritis, reactive arthritis, chronic inflammatory low back pain and other related spondylo-arthropathies have been found to have a high incidence of B27 (Sachs and Brewerton 1978, Mehra *et al.* 1982). This is suggestive of a common hereditary and pathogenetic mechanism governing the susceptibility to these diseases.

The second most prominent associations have been reported so far for the diseases with an 'autoimmune' etiology, e.g. diabetes mellitus, myasthenia gravis, addison's disease, thyrotoxicosis, etc. The reported association of HLA-B8 with type 1 insulin dependant diabetes mellitus in caucasians (Cudworth and Fostenstein 1978) and HLA-BW35 in Asian Indians (Srikantia *et al.* 1980) has been noteworthy.

Amongst the infectious diseases, leprosy and tuberculosis have been extensively studied by our own group in India. Though no meaningful association was recorded for the antigens of the SD loci, typing of HLA-DR determinants revealed a strong association between DR2 and tuberculoid leprosy, particularly the familial cases (Devries *et al.* 1980). Similar studies by us on multiple case families of pulmonary tuberculosis have revealed an association with HLA-DR2.

It has been noted that the disease associations have more frequently involved the B locus antigens than those at the A or C loci. Examination of the D-locus specificities has been even more productive and more and more associations are being presently recorded involving HLA-D/D specificities, particularly in those diseases which showed rather 'weak' associations at the HLA-B locus. These include diseases like insulin dependant diabetes mellitus with HLA-DR3 (Cudworth and Fostenstein 1978, Mehra *et al.* 1981) rheumatoid arthritis with DR4 (Stastny 1978, Mehra *et al.* 1982) multiple sclerosis with DR2 (Batchelor *et al.* 1978) etc. One might point out that B-locus is closer to the D-locus which is probably analogous to the immune response area (Ir antigens) of the mouse (McDevitt *et al.* 1976).

(d) Mechanisms underlying disease associations While the exact mechanisms of HLA and disease associations are still under extensive investigations, various possibilities can be considered. The associations found may in fact be due to change alone; a particular HLA specificity gets precipitated because of the stratification of populations, giving rise to its increased frequency in the disease process. Theoretically, this may be possible but the reported association of various diseases with a common antigen in most populations, e.g. B27 and AS suggests the contrary.

HLA antigens might provide 'receptor' sites for the infectious agents of their products, thereby providing linkage with mutants causing disease or providing positive linkage disequilibrium with genes causing decreased immune responsiveness or increased susceptibility.

Certain invading organisms might share antigenic cross reactivity or structural configuration with the HLA antigens (molecular mimicry). This would cause modification of the HLA antigens by microbes and interfere with their inner environment and finally, the possible role of the HLA antigens in the regulation of the immune response to a variety of pathogens. The recently discovered immune response (Ir) genes are pertinent candidates for the defective, altered or absent specific immune response to causal agents, pathological immune response.

Conclusions

The recent advancements in the knowledge concerning the vast complexity and biological importance of the genes and products of the major histocompatibility system, including the Ir genes, have helped the physician and the basic researchers in many ways. It has contributed to the proper understanding of the etiopathogenesis and prognosis of several diverse and hitherto complex disease entities. It has also helped in differentiating a number of disorders and has suggested a common pathogenetic link between them. This has led to a rational classification of many complex disorders and helped in understanding the underlying heterogeneity. Finally, the discovery of this rather reliable genetic polymorphism has helped the control of a number of diseases by identifying the susceptible population at 'risk' and instituting the appropriate prophylactic measures, including the immunological intervention, to mitigate the onslaught of tissue damage.

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Highlights of Group Discussions : Session II

Association of Genetic Markers with Health and Disease

Bansal : The utility of the study of genetic markers and disease associations is in their being diagnostic tools which can be used in health programmes. The implicit reliability of the associations is based on rigorous controls.

Mehra : The study of disease association with genetic markers may be viewed as long term and short term goals. Elucidation of the pathogenic mechanism behind the antigen related diseases is probably the long term goal, while its application to the patient care is the short term goal.

Tiwari : The baseline information on the genetic markers, as such and their relationship within the prevalent diseases in the country should be generated.

Agarwal : The associations between HLA polymorphisms and diseases are more acceptable from clinicians point of view although complexity of the HLA polymorphism poses problems in its wider applications.

Kalla : ABO and disease associations provide some idea about the susceptibility to a particular disease.

Roy : In many cases the results of such studies show that 60 percent of a particular blood groups are susceptible to the disease and 40 percent are akin to the normals. I wonder how this information could be utilized for promotion of health care. We should address ourselves to development of an approach whereby these associations could be of use in delineation of the high risk population groups.

Kate : We should explore the various other genetic polymorphism, keeping in view their utility as diagnostic tools.

Sukumaran : Information on association of Duffy blood groups and malaria in the African populations is available. In view of malarial endemicity in the country, data on malaria and Duffy blood groups should be collected.

Malhotra : We have to keep in mind the available facilities and the financial resources because of costly sera for rare blood groups.

Bhalla : Loss of ABH antigens in case of leukemia suggest that indepth and detailed investigations with multigene markers approach may provide more information on the disease associations. Discovery of B like antigens in E. Coli has broughtforth evidence that blood group B individuals are favourably disposed to gram negative bacteria. Further studies should be directed to elucidate the pathophysiology of the diseases associations.

Swarup-Mitra : The predominance of B blood groups in Gangetic plains has been relegated to prevalent infectious diseases in this area. Does it refer to any selective advantage ?

Bhalla : Similar evidence has been brought forth in Mongolia where malaria and smallpox has been endemic.

Mehra : Search should be made for genetic markers which could differentiate the affected individuals with strong associations and ultimately help in identification of high risk individuals/populations for which preventive measures could be initiated.

Bhalla : Proper channelisation of the information to the clinician may help in its effective utilisation in health care.

Baxi : It would be desirable that studies should be carried out to establish the associations particularly in relation to diseases which are endemic in the country and also the malignancies.

Swarup-Mitra : It would be worthwhile that studies on red cell enzyme polymorphisms, etc. may be carried out in relation to the diseases.

Agarwal : The severity of the disease is most important in relation to the capacity of an individual to launch an immune response. Simultaneous studies on (Ir) Immune response genes may elicit useful information.

Sukumaran : Cost of reagents and the antisera are the major bottlenecks in carrying out detailed investigations. However, I feel Haffkine Institute and Blood Group Reference Centre* Bombay can take up the production or import and distribution of the rare blood group sera and other reagents.

*Now known as Institute of Hematology.

Agarwal : I strongly feel no one centre can do all the things alone. Multi-centric approach is the ultimate solution. The studies should be undertaken to evaluate the pathophysiology of the disease where strong associations are known to exist and attempts towards development of intervention measures should be made.

Ahuja : Study of pathophysiology of the disease, including the biochemical parameters, hold promise since it may help in understanding the causative mechanism of the disease and thereby will provide a clue for developing curative and preventive measures.

Sidhu : The importance of a suitable control cannot be ignored. Study of disease associations in population groups, where selection intensity is of low magnitude, may provide further information on the mechanism of the disease associations.

SESSION III

Inbreeding in India : Its Genetic Consequences and Implications in Health Care

Keynote Address :

Inbreeding in India : Its Genetic Consequences and Implications in Health Care S. K. BASU

Highlights of Discussions

Inbreeding in India : Its Genetic Consequences and Implications in Health Care

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Marriage Practices

India is characterized by the presence of a large number of endogamous castes, tribes and religious communities with different types of marriage practices. The pattern of marriages in India is largely governed by three important regulations, namely (a) Endogamy (marrying within the group of birth) (b) Exogamy (marrying out) and (c) Consanguineous or Sapinda marriages. The regulation of consanguineous marriages does not permit marriages between two individuals related through a common male ancestor upto 7th generation on the father's side and 5th generation on the mother's side. The consanguineous regulation has been enforced with great rigidity in the North. But in South, it is somewhat relaxed to conform to the prevailing custom of great preference for consanguineous marriages.

Importance of Consanguineous Marriages

Studies of marriages between close relatives or consanguineous marriages offer the most interesting material for research in human genetics. A consanguineous mating is between two individuals who have one or more common ancestors. The likelihood of spouses having the same genes is considerably increased in close inbreeding. Inbreeding tends to bring into the open recessive alleles present in heterozygous carriers. Many harmful traits are recessive and are, therefore, most likely to appear in the children of parents who are closely related. Many rare diseases controlled by

recessive alleles have been or can be discovered through the study of consanguineous marriages. Simultaneously, increased risk of homozygosity for deleterious recessive mutants that occur among the offspring of consanguineous marriages may results in an increased probability of abortion, miscarriages, still births, neonatal deaths, etc. Increased risk of illness, susceptibility to diseases, physical and mental defects are usually directly correlated to the various degrees of consanguinity. It is, therefore, of utmost importance to evaluate the effects of inbreeding precisely. Studies on inbreeding have been largely limited to the investigation of the attributes of the offspring of consanguineous marriages which may be termed "Parental Consanguinity Effects". Few data are available (Schull *et al*, 1970) on the characteristics of the children born to parents who are themselves the product of a consanguineous marriage—this may be termed "Inbreeding Effects". It is essential to lay emphasis both on parental consanguinity and inbreeding so that a total picture of homozygosity effects can be obtained.

Prevalence of Consanguineous Marriages in India

In India, there is a greater incidence of consanguineous marriages leading to a high degree of inbreeding, a parallel of which is not found anywhere in the world. Geographical locations, availability of mates, various socio-economic factors like dowry, land, property, interpersonal relationship between a new bride and her mother-in-law and religious sanctions are the major factors responsible for the practice of consanguinity. Populations in Southern States of India, i.e. Andhra Pradesh (Sanghvi 1966, Dronamraju and Meera Khan (1963), Kerala (Ali 1968), Tamil Nadu (Chakravarty 1968, Rao 1978), Karnataka and Maharashtra are unique in the occurrence of a fairly high frequency of consanguineous marriages. High frequency of consanguinity has also been reported among the Muslims of Delhi and Lucknow, (Basu 1978), West Bengal (Huq 1976) and Dawoodi Bohras of Udaipur (Basu 1978), Scheduled Castes and Tribes of Madhya Pradesh (Goswami 1970). The magnitude of consanguinity effect is best measured by the frequency of cousin marriages in a population. Detailed review of the incidence of consanguineous marriages in India has been done by Chakravarti (1968), Basu (1971) and Roychoudhury (1976).

Effects of Inbreeding

The offspring of a consanguineous marriage may either have undesirable characteristics of normal or even better average constitutions. Such different results are partly due to initial genetic differences in the original mates who may be carriers of unfavourable or favourable recessive genes. It is generally known that the traits determined by rare recessive genes are more likely to appear among the offspring of consanguineous matings as compared to unrelated ones. Moreover, the probabilty of homozygosis of

recessive genes in children is higher if their parents are uncle-niece than if they are first cousins. Consequently, the children from consanguineous marriages have an enhanced risk of hereditary defects and diseases transmitted through recessive genes.

A number of studies have been carried out in the U.S.A., France and Japan to investigate the effects of consanguinity (Morton 1961, Crow 1958, Sutter and Tabah 1952, Schull 1958, 1959, 1968, Neel and Schull 1970). In general, these studies show that the rates of morbidity and mortality are increased in the offspring of consanguineous marriages, as compared to those of unrelated parents.

Our knowledge in India of the effects of inbreeding on fertility and morbidity is woefully inadequate. Findings reported by different authors are not uniform. Studies by Kumar *et al*, 1967, Murty and Jamil, 1972, Basu, 1971, 1978; Chakraborty and Chakravarty 1975, Rao and Reddy, 1977 and Reddy 1978, etc. show that the rates of mortality are increased in the offspring of consanguineous marriages as compared to those of unrelated parents. However, no effect of inbreeding on mortality has been reported by others (Rao and Inbaraj 1977, Rao 1977 etc.). Higher incidence of congenital malformations was observed (Murty and Jamil 1972, Chakraborty and Chakravarti 1975, Basu, 1978 etc.) among the offspring of consanguineous matings, while no significant effect of parental consanguinity on congential malformation was noted by other authors (Sanghvi *et al*. 1974, Rao 1976 and Rao and Inbaraj 1977 etc.).

Similarly, definite effect of consanguinity on fertility has been noted (Mukherjee and Bhasker 1974, Rao and Reddy 1977, Basu 1978, Reddy 1978) but no effect of consanguinity on fertility has been reported by others (Saheb *et al*. 1978 and Rao and Inbaraj 1979).

These contradictory findings in recent years have necessitated more careful and prospective surveys for studying the effects of inbreeding than collecting data through retrospective techniques. Moreover, the history of inbreeding may be different for each population group under study and thereby generalisation whatsoever may not be valid. History of inbreeding in a population group ultimately decides the rate of elimination of the deleterious genes (Sanghvi 1978). It is, therefore, necessary to consider both the extent and duration of practice of consanguinity so as to discern short and long term effects which will ultimately help to understand the burden of recessive deleterious genes.

Lacunae and Avenues for Future Research

(a) Hardly or consanguinity survey has been undertaken in Northern India and North-Eastern India.

(b) Data on the incidence and effect of consanguinity in tribal populations, scheduled caste groups, hilly people and minority communities are scanty and need detailed systematic study.

(c) To fill the gap of our knowledge, a survey on the pattern and prevalence of consanguinity among the Muslims in Jammu and Kashmir, Punjab and Gujarat may be undertaken.

(d) So far, consanguinity studies are confined to a few states namely Andhra Pradesh, Tamil Nadu, Kerala, Karnataka, Madhya Pradesh, Rajasthan, U.P., West Bengal and Delhi. Moreover, in these states, the investigations are largely confined to small population groups. The incidence of inbreeding in the people of other State is unknown.

(e) Degree of parental consanguinity and various determinants of consanguinity in different populations are to be explored in detail.

(f) Hospital-based consanguinity data are to be discouraged. Emphasis should be on population studies with detailed genealogies maintaining suitable control from the same socio-economic and ethnic group.

(g) Temporal trends of consanguinity need to be evaluated.

(h) More large scale and intensive studies are needed among different population groups to evaluate the effects of both "parental consanguinity" and "inbreeding" with special reference to early foetal deaths, fertility, reproductive compensation, intelligence, mental traits, susceptibility to diseases, maternal mortality, physical development, blood pressure, vision and hearing and congenital malformations.

(i) While studying the effects of inbreeding, special attention should be paid to prospective surveys, history of inbreeding (extent and duration of practice of consanguinity– both short and long term effects) which will finally help to understand the burden of recessive deleterious genes in human populations. These will help in developing proper genetic counselling and arriving at empirical risk estimates.

Consanguinity and Community Health

Studies on consanguinity and its effect on fertility, mortality and morbidity in different inbred communnities will generate sufficient genetic information to provide guidelines in determining the nature and extent of health and family welfare programme for these inbred groups. These studies will also provide requisite information for counselling, motivation and genetic education purposes in high risk families.

Detailed study of effects of inbreeding would enable voluntary restriction of child bearing by couples who have been found to carry serious hereditary defects.

Considerable burden in the form of deleterious recesssive genes is added to the community as a whole because of prevelent practice of consanguinity. W. H. O. technical committee (1964) expressed the following view on the subject

> "It would be advantage to the health of the community if these frequencies (of consanguineous marriages) should diminish. All else being equal—and, of course, social and other considerations are important—an outbreeding human population is a healthier populations and this is not only because of a falling off in definite, known, recessively determined defects".

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Highlights of Discussions : Session III

Inbreeding in India : Its Genetic Consequences and Implications in Health Care

Roy : Increased incidence of reproductive wastage among the consanguineous groups have been reported in studies carried out at this Institute. How far other regions and areas of the country, despite the environmental, nutritional and other variations, correspond with the above findings would be worthwhile to study. New vistas have to be created to utilize the information on effects of inbreeding.

Ahuja : Variability in the effects of inbreeding in different population groups can be ascribed to the relative frequency of the deleterious alleles in the gene pool.

Basu : Dr. Sanghvi's data bear out that the variability of the effects of inbreeding can be traced to the histroy of inbreeding.

Bardhan : Decade-wise analysis of the data on consanguinity and its effects may provide useful information on temporal trends and subsequently the information on genetic load could be obtained. This information can be used for initiating preventive and promotive aspects of health care.

Basu : Variation in the degree of inbreeding and its subsequent effects have to be studied separately as our experience from studies among Dawoodi Bohras and Shia Sunni Muslims of Udaipur and Lucknow suggests. A standard genealogical approcah is essential.

Das : Muslims of Assam do not practice consanguinity at all. Standard genealogical approach may yield additional infcrmation on the genetics of many disorders.

Kalla : In Jammu and Kashmir, some recent converts to Islam still follow the Hindu system of arranged marriages.

Basu : This may be true for muslims and other caste groups that did not practice inbreeding initially but adopted it at later stages. This information is crucial for evaluating the effects of inbreeding. Another important lacuna in the available studies on the effects of inbreeding is that generally they have been carried out on the hospital sample. This, I feel, is not a correct approach.

Swarup Mitra : Socio-economic factors are probably of prime importance to promote the practice of inbreeding and consanguinity. While evaluating the effects of inbreeding, socio-economic factors, including nutritional and environmental characteristics, should be considered.

Malhotra : A large number of studies from different parts of the country have thrown up often contradictory results for various reasons. Our knowledge on consanguinity in India is not complete, because of not taking into account the history of inbreeding. A suitable control is of utmost importance in evaluating the effects on fertility, mortality and morbidity, with due consideration being shown to the socio-economic variables.

V. Bhalla : Rigid sampling procedure has to be followed along with using proper controls for valid comparisons. It would be worthwhile to initiate prospective studies to understand the effect of consanguinity and inbreeding, specially on congenital malformations and other morbid conditions.

Malhotra : Information collected through reliable methods will increase the validity of information and it can be effectively used in calculating the risk figures for the Indian population groups.

Sukumaran : Keeping in view the diversity of the Indian population groups and their geographical location, etc. a multicentered and multidisciplinary approach should be appropriate.

Bhalla : Working group meetings can be organized to out line a standard approach.

Kalla : The results of such controlled studies can be utilized in creating mass awareness on the effects of inbreeding and consanguinity.

Agarwal : The knowledge on the effects of inbreeding and consanguinity should be disseminated with due caution. We should not raise the expectations of the population groups wtithout creating in advance proper infrastructure to meet them.

Malhotra : Moreover, the situation will be different in different regions as well as population groups. Individual characteristic guidelines and methodology of orientation will have to be developed.

SESSION IV

Genetico-Environmental Studies on Indian Tribes — Consideration of Approaches for Promotion of Health Care

Keynote Addresses :

Medicogenetic Problems of the Tribal Communities of India I. P. SINGH

Demographic Trends of the Tribals P. PADMANABHA

Highlights of Discussions

Medico-Genetic Problems of the Tribal Communities

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Health planning, a concept of recent origin, seeks to meet the health needs and demands of the people. Health needs as seen by the people are not exactly the same as perceived by health planners. Some needs may not be perceived at all, others vaguely perceived and still others awaken only on contact with new ways of life.

According to 1981 census, the population of India has been estimated to be 683, 810, 051, of which scheduled tribes together with scheduled castes constitute about 21 percent. The scheduled tribe population in the country, comprising 250 scheduled tribal communities, is about 4 Crores. Major tribal groups account for about twenty million or two crores of scheduled tribes. They include approximately 52 lakhs Bhils, 48 lakhs Gonds, 36 lakhs Santhals, 17 lakhs Oraons, 15 lakhs Meena, 12 lakhs Munda, 9 lakhs Khonds, 5 lakhs Ho and 5 lakhs Nagas. At the other end of the spectrum, there are over 50 small tribal groups, ranging from the smallest group of 25 Great Andamanese souls to the largest of about 2 lakhs, the other groups in between consist of a few thousands only. The total population of these groups does not exceed 10 lakhs.

These communities are at various levels of cultural, social, economic and political development. On the basis of economic criteria the Indian tribes can be divided into three classes. There are tribes living in hills and jungles and have little contact with outside world. They are still in the hunting and food gathering stage, and are found in pockets of South and Central India and Andaman Islands. Another class is of these freedom-loving and politically conscious tribals of the North-East who can rub shoulders with their most enlightened counterparts among the economically advanced communities.

In between these two groups are included communities which are at varying levels of development inhabiting the central Indian belt.

In spite of certain special measures taken, the proportion of certain tribes has not increased significantly (Table 1) because of poor health status of these communities. This problems can only be studied through an approach which should be multidisciplinary and should yield information simultaneously on the following aspects :

(i) a basic socio-demographic profile of the communities, especially morbidity and mortality statistics.

(ii) medical status of the subjects;

(iii) nutritional and environmental conditions;

(iv) a general survey of the genetic conditions;

(v) dental condition;

(vi) an assessment of physique and growth;

(vii) working capacity as an index of fitness;

(viii) a basic assessment of the environment.

Health and sickness surveys provide comprehensive data about the health and morbidity status of the population as a whole. Morbidity surveys are usually done on a representative sample of the population because surveys of the total population are not only expensive but may not be feasible. Mortality statistics give a fair picture of the distribution of disease as a cause of death but they cannot provided an estimate of the load of sickness and disability that preceeds death. In many chronic cases of low fatality (e. g., mental diseases, arthritis, etc), mortality statistics are virtually useless (WHO. 1967). Morbidity statistics provide better statistics as an index of sickness and health, than mortality. The causes of slow growth rate of these populations can only be understood by undertaking indepth studies of the following aspects :

Demographic charactsistics

Mortality

Morbidity

Health status

Table 1

Some numerically smaller tribes of India according to 1961 and 1971 census

State	1961	1971
U. P.		
Jaunsaris	Not available	56,699
Tamil Nadu		
Kurumbas	1174	2744
Paniyans	4779	6093
Palayan	2669	4308
Toda	714	930
Kerala		
Kadars	957	1120
Irulas	11954	14852
Bihar		
Birhor	1438	3464
Andaman Island		
Onges	129	112
Shompens	71	92
Nicobarese	13,903	17,874

Demographic Characteristics

The demographic profile of India is characterised by a birth rate of 34.5 per 1,000 (Centre Calling 1977). The population is increasing at the rate of one million a month (NIHAE Bulletin 1977). The current annual growth rate of the population is estimated to be 1.9 percent (Centre Calling 1977). There is a disproportionately large number of children (40 percent) below the age of 15 years, and a low proportion of people living beyond middle age.

The density of the population per sq. km is 185. The sex ratio in the majority of states is in favour of males. The overall literacy rate of the population is 36.17 percent (Census of India 1981).

Mortality

The general mortality is 14.5 per 1,000 population (Population Reference Bureau Inc. 1981) compared with less than 10 in developed countries. The life expectancy at birth is estimated to be 52 years for males and 51 years for females. Corresponding figures for the developed countries average 70 years for males and 75 years for females. Infant mortality is estimated to be 120 per 1,000 live births, whereas in Europe it is less than 20 per 1,000 live births and even below 10 per 1,000 in some countries. Mortality in the age group 1-4 years is around 30 per 1,000 as against less than 1 per 1,000 in developed countries. Information on causes of death is incomplete. Records show that infective and parasitic diseases account for 15-25 percent of deaths in India (Sen Gupta and Kapoor, 1970).

Morbidity

The principle causes of morbidity are as follows :

Infective and parasitic diseases

Malnutrition

Non-communicable diseases

Sickness load

Beside these parameters, the association of different genetic markers with morbidity pattern also needs to be investigated.

Infective and parasitic diseases

These are responsible for about 60 percent of hospital admissions (Centre Calling 1977). Among the viral diseases, measles continues to be rife among children. Polio is frequent in India and so is viral hepatitis. Among the bacterial diseases, enteric fever, diarrhoea, dysentry and cholera are endemic owing to inadequate sanitation. The prevalence of tuberculosis is high with a morbidity of 4 (bacteriologically confirmed cases) per 1,000 population (WHO 1974). The number of known cases of leprosy in India is 3.2 milion (WHO 1975). Among the parasitic diseases, malaria and kala-azar have reappeared in a big way. Intestinal parasites are too frequent. In addition to these, there are the infectious diseases of childhood, acute respiratory and gastro-intestinal infections and the sexually transmitted diseases.

Malnutrition

Malnutrition is an important cause of morbidlty. One to two percent of children below 5 years suffer from protein-calorie malnutrition (Swasth Hind 1974). Nutritional

anemia is widespread not only among women of the reproductive age group, but also pre-school children. Avitaminoses, particularly Xerophthalmia and endemic goitre are important public health problems in certain parts of the country. All these represent only a minor fraction of the extent of malnutrition existing in the country.

Non-communicable diseases

Non-communicable diseases, such as, ischaemic heart disease and cancer are already posing a problem in some social groups. Occupational diseases such as silicosis and other pneumoconioses are on the increase. Environmental pollution, alcholism and allergic disorders are emergent problems.

Sickness load

Surveys have shown that as much as 7-13 percent of the rural population may be sick at any given time. On an average the number of new incidence of sickness per person per year was found to be ranging between 2.6 and 3.9 Swasth Hind 1974).

Association of Genetic Markers with Morbidity

Genetic markers and abortion

Quite often, there is production of antibodies by the mother in response to the presence of antigens which the fetus inherits from the father and which the mother lacks, e.g. Rh factor. The antigen usually gets into the maternal circulation through the placenta. The antibody produced by the mother filters back into circulation of the fetus and damages or destroys the red cells of the fetus. This results in hemolytic disease of the newborn, known as Erythroblastosis Fetalis. This disease is so severe in many cases that the still birth results or the infant dies shortly after birth.

There are two types of matings with reference to presence of blood group antigens. These are homospecific and heterospecific. Homospecific matings are those in which the female either has the same red cell antigen as the male or has no specific antibody in her blood serum for the antigens of the male and is not capable of producing one. In heterospecific matings the female either has an antibody present in her blood serum for the red cell antigens of the male or is capable of producing such an antibody. Heterospecific pregnancies are those in which the female either has or can produce an antibody to the red cell antigens of the fetus she carries. A heterospecific mating, for example, is one between a male of blood type A and a female of blood type O or B. The female carries in her serum anti-A antibody which will agglutinate the red cells of her husband, and, if she has a fetus of blood type A, she carries an antibody antagonistic to the red cells of her fetus. This type of ABO incompatibility accounts for a large number of fetal deaths.

Association of genetic markers with diseases

It has been observed that the children of blood group A appeared to be at greater risk of dying from bronchopneumonia than those of other groups. An excess of individuals of blood group O and a deficiency of those of group A has been observed among people suffering from A_2 influenza virus infection (Mcdonald and Zuckerman 1962). An opposite trend was found in subjects with adenovirus infections. Zuckerman and McDonald (1963) tested the blood groups of 378 cases of infective hepatitis and found an excess of group A individuals. It has been shown by Vogel and Chakravarti (1966) that individuals of blood group A or AB were much more liable to develop smallpox than those of groups B and O and, moreover, the course of the disease tended to be more severe in the former. The mortality was significantly higher in individuals possessing the blood group A gene than in those with other blood groups. Support for their findings comes from the work of Bernhard (1966), who compared the variations in ABO gene frequencies in different areas of India and Pakistan with the varying mortality from smallpox in those areas. He found a significant inverse relationship between the frequency of A gene and smallpox mortality. This is consistent with a strong selective pressure against the A gene in areas of smallpox endemicity.

HLA and specific diseases associations

There have been several reports indicating an association between HLA and certain diseases in which bacterial and viral infection play an important role. This has been suggested for a number of arthritic diseases preceded by infections in the pathogenesis of ankylosing spondylitis. Following the findings on the role of H-2 in viral oncogenesis, human malignant diseases were studied. Initial investigations showed only weak correlations. Recently a highly significant association between an HLA antigen BW 46 with nasopharyngeal carcinoma was found almost exclusively among Chinese population groups. When other non-malignant diseases are considered, there are some very striking associations. This is particularly noticeable with diseases having a presumptive or suspected immune etiology, including psoriasis and several rheumatological disorders.

Chromosomal abnormality as a cause of morbidity

The incidence of chromosomal abnormalities as a cause of morbidity is very high (Carr 1967, Jacobs 1972, Boue and Boue 1973, Salisbury *et al*. 1977). Chromosomal abnormality in a male may result in defective spermatogenesis leading to oligospermia and asthenospermia. In some instances, in spite of carrying a defective chromosomal complement, the sperm may be functionally active and be capable of fertilising the ovum. The result would then be the production of chromosomally unbalanced zygote. This may lead to either spontaneous abortion or congenital malformations. On the other hand, the cytogenetically abnormal spermatozoa may be incapable of fertilising

the ovum, thus leading to infertility. Reproductive failure, either in the form of repeated abortion or as infertility, may be nature's way of preventing defective offspring.

The frequency of chromosome abnormalities in couples with reproductive failure ranges from 1/10 (Kim *et al.* 1975) to 1/30 (Tsenghi *et al.* 1976). The higher incidence figures are attributed to exact identification of balanced chromosome rearrangements using the newer banding techniques (Kim *et al.* 1975). It is estimated that in about 1 in 700 apparently normal individuals is a carrier of a translocation. Cytogenetic studies of families with reproductive failure have shown a tenfold increase in the frequency of translocation as compared to the general population (Hamerton, 1971). Thus reproductive failure in the absence of any specific apparent cause, signals the need for a cytogenetic investigation using the new banding techniques.

The introduction of banding techniques has revealed a wider spectrum of karyotypic variation (heteromorphisms) as compared to conventional staining techniques. The karyotypic heteromorphisms detected in human chromosomes are associated with constitutive heterochromatin localized near the centromere of every chromosome and the distal part of the long arm of Y chromosome. Individuals with extremely polymorphous heterochromatic regions may show a decreased relative reproductive fitness and there may be an increased risk of chromosome abnormalities in the progeny (Holbeck *et al.* 1974, Jacobs *et al.* 1975). Spontaneous abortion may be caused by an imbalanced state of heterochromatic regions in the embryo which may result due to disturbed segregation of these variant chromosomes during meiosis (Tsenghi *et al.* 1976). A significantly higher frequency of carriers of an enlarged secondary constriction of chromosome 9 (9b+) has been reported among parents of abortuses with abnormal karyotypes as compared with parents of abortuses with normal karyotypes (Lauritsen and Therkelsen 1977). An association between long Y chromosome and fetal loss has also been observed (Patil and Lubs 1977). These heteromorphisms can contribute to abnormal disjunction or in some other way endanger development in the sense of a "structural genetic load" (German *et al.* 1966).

Health Status

There was one doctor for 4,000 population and one nurse for 6,300 population at the end of 1974-1975 (Govt. of India, Pocket Book of Health Statistics of India 1977). Corresponding figures for USA were 1:600 and 1:60. The bed population in India was 0.6 per 1,000 population (NIHAE Bulletin 1977). Health care for the rural population, which makes up 80 percent of the population, is provided by primary health centres and sub-centres, each PHC catering to a population of nearly cne lakh and a subcentre catering to a population of 10,000. Health facilities in metropolitan cities are close to the level found in industrialized countries. The Government expenditure on

health services is between 3-4 percent of total expenditure per capita health expenditure (1973-1974) was Rs. 7.72 as compared to Rs. 47.4 in U.K. (Govt. of India, Pocket Book of Health Statistics of India 1977).

Health Planning

The investigation into the physical well being of scheduled tribes can be done in terms of their health and disease status and the indicators used for this purpose need to be evaluated (WHO 1971, Sharma 1969). Planning, which involves a succession of steps, is based on correct description of health needs, acceptance of long term and short term objectives and goals, assessment of resources, the extent of implementation and finally proper evaluation of the performance.

The implementation of any health plan depends upon how effective is the existing organization. Many well framed plans have failed because of delays in critical supplies, inadequacy of staff motivation and training in the existing organisation to deliver health services.

Evaluation of the plan performance should be undertaken with reference to the degree to which objectives and targets are fulfilled and the quality of results obtained. The productivity of available resources should be measured in terms of achieving clearly defined objectives so as to make it possible for priorities and resources to be reallocated on the basis of changing health needs (WHO 1967).

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Demographic Trends of Tribals

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Registrar General and Census Commissioner, Govt, of India. New Delhi

The term 'Tribe' is nowhere defined in the Constitution and in fact, there is no satisfactory definition anywhere. No standard term has been accepted to denominate the people who are classified as of tribal origin. According to Article 342 of the Constitution, the scheduled tribes are the tribes or tribal communities which may be notified by the President. The Census enumerates only such tribal communities as are scheduled under the relevant Constitutional order in force at the time of the Census.

The Census of 1971 enumerated the population of scheduled tribes as 38 million, comprising 6.94 per cent of the total population of the country. This population is unevenly distributed in various States and Union Territories. The largest population is found in Madhya Pradesh (8.39 million). But their largest proportion to total population is found in Nagaland (88.61 per cent) followed by Meghalaya (80.48 percent). Among Union Territories, Lakshadweep (92.86 percent) ranks first followed by Dadra and Nagar Haveli (86.89 per cent), and Arunachal Pradesh (79.02 percent). There are no scheduled tribes in Haryana, Jammu & Kashmir, Punjab, Chandigarh, Delhi and Pondicherry.

Taking into consideration the pattern of distribution of the scheduled tribes, the Government of India has carved out certain areas where they constitute at least half of the total population and declared them as scheduled areas and tribal areas under Article 244 (Fifth Schedule and Sixth Schedule) of the Constitution. These areas, which may cover a district, a tehsil or even a smaller unit, have been constituted in Andhra Pradesh, Assam, Bihar, Gujarat, Himachal Pradesh, Madhya Pradesh, Maharashtra, Meghalaya, Orissa, Rajasthan and Mizoram. Thus, the scheduled tribes form blocks of various sizes

generally in the interior inhospitable terrains. Even in the areas where non-tribals preponderate, the scheduled tribes are generally concentrated in identifiable pockets.

Sex Ratio

As compared to the general population, there appears to be a more even distribution of males and females among the scheduled tribes. According to 1971 census their sex ratio is 982 against 930 in the general population. Both these ratios show a downward trend as compared to the 1961 ratios. The sex ratio of the tribal population of the country as a whole has gone from 987 to 982. Not unexpectedly, the sex ratio of the scheduled tribes varies in different states, the highest being in Manipur (1009) among the States, and Lakshadweep (1021) and Mizoram (1021) among the Union Territories. The rural-urban distribution also follows the same pattern as in the general population, i.e., it is higher in the rural areas and lower in the towns. Table 1 shows the broad age-group-wise and sex-wise percentage distribution of scheduled tribes and the general population of the country as a whole as in the 1971 Census. By and large the sex-wise distribution is similar to the general population in the country.

Table 1

Category of Population	Broad age groups								
	0-14			15-44			45+		
	P	M	F	P	M	F	P	M	F
General Population	42.02*	41.86	42.19	41.73	41.46	42.03	16.23	16.66	15.76
Scheduled Tribe Population	44.06	43.95	44.18	41.22	40.95	41.50	14.70	15.09	14.30

*Percentage

However, in Andhra Pradesh, Kerala, Tamil Nadu and Andaman & Nicobar Islands, the sex ratio is lower among the scheduled tribes than among the general population. The sex ratio among scheduled tribes is highest in Lakshadweep and Mizoram, viz., 1021 in each case, while the lowest is 880 in Uttar Pradesh. The largest difference in the sex ratio between the general population and scheduled tribes population is found in West Bengal, where the ratios among the general population and scheduled tribe population are 891 and 955 respectively.

Rural-Urban Distribution

Table 2 shows the percentage of rural and urban dwellers among the scheduled tribes and the general population of the country as per the 1961 and 1971 censuses.

Table 2

Census Year	General Population		Scheduled Tribe Population	
	Rural	Urban	Rural	Urban
1961	82.03	17.97	97.31	2.59
1971	80.09	19.91	96.59	3.41

Despite the growth of townships and industrial complexes in the midst of tribal habitats, the tribals by and large are not affected by the urbanisation process. The rural population of scheduled tribes constitutes 96.59 per cent of total population, as against 80.09 per cent among the general population. It is, however, seen that like the general population of the country, the proportion of the rural population among scheduled tribes has gone down slightly during the 1961-71 decade. The proportion of rural/urban populations also shows some variations in different States and Union Territories.

Age at Marriage

Data on age at marriage are available only in respect of a few individual scheduled tribes. The 1971 Census data on married and divorced/separated persons in the 0-14 age group, presented in Table 3, gives some idea about proportion of early marriage.

Table 3

Category	Total population in the 0-14 age-group (in thousands)			No. of married, widowed/ divorced persons in the 0-14 age-group and their percentage to total population (in thousands)		
	Persons	Males	Females	Persons	Males	Females
General Population	230,334	118,908	111,426	5,406 (2.35)	1,655 (1.39)	3.751 (3.37)
Scheduled Tribe Population	16,742	8,425	8,316	328 (1.96)	110 (1.31)	217 (2.62)

Figures in parenthesis indicate percentage.

A higher percentage of married and divorced persons (2.35 percent) is noticed in the 0-14 age group of general population as compared to scheduled tribes (1.96 percent). In fact, the lower percentage of married persons among the scheduled tribes is primarily due to proportionately less married women in the same age group in comparison to the general population. Tribal women apparently marry late as compared to the others.

During the 1971 Census, information was tabulated for the first time on age at marriage for currently married women on the basis of a 10 percent sample of individual slips for the rural areas and 20 percent sample for urban areas. The data *inter alia* present statewise mean and median age at marriage in respect of scheduled tribe category, separately for rural and urban areas. The mean age at marriage in the case of scheduled tribes (16.39) is found to be substantially higher than the mean age at marriage (15.39) for the general population in the rural areas. The mean age at marriage for scheduled tribes is also higher than those for Hindus, Muslims, Buddhists and Jains.

Education and Literacy

According to the 1971 Census data, the general literacy in case of scheduled tribes is very low, 11.30 percent only against 29.45 per cent literacy in respect of general population. Most of the literates among the scheduled tribes are literates upto primary level. The proportion of literates who have attained matriculation or above levels is insignificant. The percentage of literacy varies from the lowest 5.34 percent in Andhra Pradesh to 26.45 per cent in Meghalaya among the states. The proportion of scheduled tribe population in Meghalaya is quite high in the total population. In Kerala, the literacy in case of scheduled tribes is 25.72 percent against 60.42 percent for the general population. Among the Union Territories, the highest literacy in case of scheduled tribes is found in Mizoram (53.49 percent), as against 5.20 percent in Arunachal Pradesh.

Workers and Occupational Pattern

There is a decline in the proportion of workers, particularly female workers, among the scheduled tribes as well as the others if the 1971 census data are compared with that of 1961. This is apparently due to different definitions adopted for workers during these censuses. There appears to be, however, little doubt that the proportion of workers is higher among scheduled tribes as compared to the others. Likewise, the female participation rate in economic activity is higher among the scheduled tribes. This is substantiated by the 1971 census data according to which the percentage of workers among the scheduled tribes is 38.47 against 32.91 in the general population. As

regards female workers, their percentage in respect of the scheduled tribe population is 20.75 against 11.85 for the general population.

Tribals in the rural areas depend on agriculture for occupation. The largest percentage of workers (90 approx.) are found in the agricultural sector ; 57.56 percent cultivators and 37.04 percent agricultural labourers. The proportion of workers among scheduled tribes in these two categories is higher as compared to that in the general population. A noteworthy feature is that during the 1961-71 decade the proportion of agricultural labourers among scheduled tribes has gone up as their percentage increased from 19.71 percent in 1961 to 33.04 percent in 1971.

Language and Mother Tongue

The 1971 census enumerated about 140 distinct tribal languages/dialects spoken by more than 19.18 million tribals as their mother tongue. In other words, nearly half the tribal population speak distinct mother tongues of their own and the rest the regional languages. Numerically, the Santhali, Gondi and Bhili dialects are spoken by largest number of persons, viz., 33 lakhs, 15 lakhs and 12 lakhs respectively.

Distribution of Population by Religion

Table 4 shows the distribution of tribal population by religion in the 1971 data. The scheduled tribes have been mostly returning themselves as Hindus (87.21 percent).

TABLE 4

Religion	Persons	Percentage of total scheduled tribe population
Buddhists	1,68,736	0.45
Christians	25,03,963	6.59
Hindus	3,31,38,960	87.21
Jains	735	Negligible
Muslims	73,700	0.19
Sikhs	229	Negligible
Tribal religions etc.	21,11,718	5.56

A fairly large number followed Christianity (6.59 percent). A significant percentage (5.56) returned distinct tribal religions, etc. (identified with the name of the tribe in many cases). The scheduled tribes had a higher percentage of Hindus and Christians, as compared to the general population. It may, however, be mentioned that christianity is more pronounced in eastern states, like Nagaland and Manipur.

Socio-cultural and Ethno-demographic Aspects

The scheduled tribes are at different stages of social, cultural and economic development. The cultural pattern varies from tribe to tribe and region to region. Agriculture is practiced by the largest number. A few follow occupations like mining, plantation, cottage industries, fishing and animal husbandry. The more backward communities, like the Onge, the Jarwa and the Andamanese of Andaman Islands, the Birhor of Bihar, the Malapandaram and the Arandan of Kerala are practically in the food gathering and hunting stage of economy. On the other hand, the communities like the Lushai and the Khasi of Assam and Meghalaya are fairly advanced and have made significant progress. The Dhodia and the Dubla of Gujarat and the Mina of Rajasthan are hardly distinguishable from their neighbours in respect of agricultural practices and some other aspects.

The racial or ethnic composition of scheduled tribes is important, because the genetic factors are expected to have a bearing on the levels of fertility. The scheduled tribes exhibit considerable heterogeneity in their composition. Broadly speaking, they fall in three groups, viz., (i) the Negroids, (ii) the Mongoloids, and (iii) the Proto-Australoids although there have been admixtures of these in varying degrees with the other ethnic types, particularly the Mediterranean. In fact, the latter element is quite common among some of the scheduled tribes, like the Mina of Rajasthan.

The geographical propinquity and demographic characteristics permit a regional and zonal classification. Broadly speaking, four main zones of scheduled tribe population can be demarcated in India. To a certain extent, the scheduled tribes in the different zones are distinguished from one another in language, culture and physical characteristics. These linguistic, cultural and racial distinctions among these tribes, however, do not appear to be accidental but are based on the nature, original source and chronological order of their migration into the country.

North ; North-Eastern Zone

This zone covers Arunachal Pradesh, Assam, Meghalaya, Mizoram, Manipur, Tripura and the Himalayan belt of Himachal Pradesh and Uttar Pradesh besides Darjeeling

district of West Bengal. The tribes of this zone mostly belong to the Mongoloid racial stock. Judging from the distribution, archaeological and other evidence, it seems probable that most of them may have migrated to India at a fairly early time, although not as early as the tribes in the other zones. They speak mostly Tibeto-Burman languages. A few like the Khasi speak Mon Khmer languages. Except in Arunachal Pradesh, these tribes are at a considerably advanced stage of development. The percentage of literacy is higher among these tribes and it can be favourably compared with the general literacy in India. As against 29.45 per cent general literacy, the literacy in case of the scheduled tribes of Assam, Manipur and Mizoram is 26.03, 28.71 and 53.49 percent respectively. The literacy in case of scheduled tribes of Mizoram is even higher than that among the general population of the country. Nagaland and Tripura have, however, registered somewhat lower literacy, 24.01 percent and 15.03 percent respectively. But even in these two areas their literacy is higher than the average literacy of 11.3 percent for the scheduled tribes in the country as a whole. The Union Territory of Arunachal Pradesh, however, contains some of the educationally most backward tribes.

A number of tribes in this zone are traditionally shifting cultivators, especially the Naga tribes. Terrace cultivation has, however, made good progress among the scheduled tribes of this region, particularly in Manipur. Some of the tribes, like the Garo and the Khasi are traditionally matrilineal, while some others, such as the Naga tribes are strongly patrilineal. The latter outnumber the former. Among the tribes of Arunachal Pradesh the important ones are the Aka, the Abor, the Miri, the Mishmi, the Dafla, the Apatani, the Galong, the Padam, the Sherdukpen, the Tagin and the Khampti. The Naga tribes live mostly in Nagaland and Manipur. The Chin and Kuki, etc. live in Manipur. Each of these tribes generally forms a territory of its own and is confined to certain areas. Some of the tribes of Himachal Pradesh, such as the Bhot of Lahaul, have a tradition of fraternal polyandry.

Central Zone

The Central zone is spread over the States of West Bengal (except Darjeeling district), Bihar, Madhya Pradesh, Eastern Maharashtra, Orissa and some parts of Andhra Pradesh. The scheduled tribes in this zone form the largest assemblage of India's tribal population comprising 58.33 per cent of total scheduled tribe population. Among the important tribes, mention may be made of the Gond, the Santhal, the Munda, the Oraon, the Ho, the Khond, the Bhumij, the Birhor and the Korku. The Gond and the Santhal numerically rank second and third respectively among all the scheduled tribes of India, each numbering about 4 miliion or more. The tribes of this zone mostly belong to Proto-Australoid racial stock. In some cases, however, their physical features have

changed in varying degrees as a result of miscegenation with the neighbouring communities. They still speak distinct languages of their own. These tribes are mainly agriculturists and while the Santhal, the Ho, the Munda and the Oraon are good plough cultivators, the Baiga of Madhya Pradesh, the Savara, the Kottia Khond and the Juang of Orissa are shifting cultivators. Only a few tribes such as the Birhor and the Korwa, depend on food gathering and hunting for their livelihood. A number of them have totemistic clans. These tribes have undergone a good deal of acculturation due to contact with their Hindu neighbours. The community life among these tribes is comparatively well organised.

Western Zone

The Western Zone comprises Western Maharashtra, Rajasthan, Gujarat, Dadra and Nagar Haveli and Goa, Daman & Diu. Some of the important tribes of this zone are the Bhil, the Dubla, the Warli, the Dhodia, the Seharia and the Mina. The tribes of this region appear to be racially much mixed. While in the Bhil group, the basic racial element Proto-Australoid is fairly pronounced, in the Mina, the Mediterranean features are pronounced. The scheduled tribes in this zone are on the whole good cultivators.

Southern Zone

This comprises Andhra Pradesh (except Visakhapatnam and Srikakulam districts), Kerala, Karnataka, Tamil Nadu and Lakshadweep Islands. The tribes of this zone, numerically not significant are the most primitive and backward among the tribes of India. Ethnically, they belong primarily to the Proto-Australoid stock. They speak Malayalam, Tamil, Telugu or Kannada or Coorgi according to the georaphical territory they occupy and the people with whom they interact. A number of them, until recently were food-gatherers and hunters without having any properly settled life. Some of them combined food gathering and hunting and some followed shifting cultivation. The tribes such as the Muduvan, the Kannikar, the Irular, the Sholaga, the Malasar and the Kadar are representatives of this phase. However, rubber, coffee and tea plantations, which have come up in these areas during the last five decades or so, employ a number of them as labourers. As a result socio-cultural and economic changes have occurred in the life of these people. Except the tribes like those belonging to the Nilgiri Hills, many of the tribes of this area, particularly that of Kerala, have matrilineal tradition. The scheduled tribes in Lakshadweep are Muslims and they follow mostly matrilineal traditions.

Apart from the scheduled tribes in the above four zones there are a few more tribes which are concentrated in Andaman and Nicobar islands in Bay of Bengal. The tribes of

Andaman, though numerically insignificant, are considered to be one of the most 'primitive' tribes. These include the Onge of Little Andaman and the Jarawa, mainly settled in the South Andaman, and the Sentinalese, who inhabit the North-Sentinal Island. The Jarawa and the Sentinalese are, however, mostly hostile and regular contact with them has not been possible to establish.

Variation in the Population Size

An important factor which has a bearing on the population growth and fertility is the bewildering variation in population size of the individual scheduled tribes, ranging from a handful of five persons to more than 5 millions.

Table 5 shows the population of ten larger scheduled tribes in order of their numerical strength and 10 tribes which constitute the smallest population groups among the

Table-5

Numerically large tribes				Small tribes			
	Community	1971 Population	1961 Population		Community	1971	1961
1.	Bhil	51,82,625 (13.63)**	38,36,308 (12.84)	1.	Arandan	5	44
2.	Gond	48,09,164 (12.65)	39,91,767 (13.36)	2.	Kochu Velan	8	47
3.	Santhal	36,33,459 (9.56)	31,54,107 (10.56)	3.	Rona, Rena	12	23
4.	Oraon	17,06,091 (4.49)	14,47,429 (4.84)	4.	Andamanese	24	19
5.	Mina	15,33,513 (4.03)	11,55,916 (3.87)	5.	Sentinalese*	82	50
6.	Munda	11,63,338 (3.06)	10,19,098 (3.41)	6.	Shompen*	92	71
7.	Khond	9,11,835 (2.40)	8,45,944 (2.83)	7.	Onge	112	129
8.	Boro, Boro-Kachari	8,67,017 (2.28)	6,72,539 (2.25)	8.	Malak-kuravan	275	248
9.	Savara/ Saora	7,82,194 (2.06)	4,32,075 (1.45)	9.	Jarawa*	275	500
10.	Varli	4,61,058 (1.21)	3,74,164 (1.25)	10.	Toda	945	716

*Estimated population **percentage

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scheduled tribes. The numerically large tribes are arranged in descending order, while the small ones are presented in ascending order. The figures in brackets show the percentage of individual scheduled tribe to the total scheduled tribe population in the case of large tribes only. In the case of minor tribes the percentages are very insignificant and can only be reflected in decimals. The ranking in both cases is on the basis of the 1971 Census only.

This table brings out that the numerical strength of the individual scheduled tribes ranges from 5 Arandans of Kerala to more than 5 million Bhils. The first three large communities, the Bhil, the Gond and the Santhal, together constitute 36 percent of the total scheduled tribe population, comprising 260 communities. If the population of the next three scheduled tribes in order of their ranking, the Oraon, the Mina and the Munda, is also added to the first three, these account for nearly half the scheduled tribe population (47.5 percent).

Population Growth

The census of India has been providing population figures of tribal communities from the very beginning. Before 1951 census, however, there was no specific list of tribes. Therefore, the data on their population growth was not fully comparable. It was for the first time in 1951 census that their population was enumerated according to a statutory list of scheduled tribes. The 1951 census, however, tabulated population of all the scheduled tribes as a category, as a whole, except in West Bengal where the population of individual scheduled tribes was also tabulated. Table 6 throws some light on the population trend from 1951 to 1971. The estimated figure for 1951 was 22.5 million. The next census (1961) enumerated the population of scheduled tribes as 30.1 million, showing an increase of 33 per cent over the previous estimated figure of the 1951 census. The growth rate was obviously very high as compared to 21.5 percent growth rate for the general population of the country during the 1951-61 decade. The percentage of increase of the scheduled tribe population could not be expected to be much higher than that of the general population. One of the reason which may explain this higher growth rate may be that when the 1956 order on scheduled castes and scheduled tribes superseded the 1950 Order, in the absence of actual census count in that year the estimate of scheduled tribe population may have been on the low side. The migrations, restriction in the area of notification in respect of a number of scheduled tribes and specification of the same community as a scheduled tribe in one area and as a scheduled caste in another made it difficult to arrive at precise estimates. The 1971 enumeration of scheduled tribes was, however, carried out as per the 1956 Order which had formed the basis of enumeration in 1961 census also. It is, therefore, possible to make a comparison of 1961 data with these of 1971. The population of scheduled

tribes registered an increase of 7.9 million (26.2 percent) from 30.1 million in 1961 to 38 million in 1971. Their slightly higher growth rate than that of the general population (24.8 percent) during the corresponding period should discount the nation of any general decline in the population of the scheduled tribes as a category. Barring a few tribes, fertility is fairly high.

Table 6

Census Year	Scheduled Tribe Population (in millions)	Total Population (in millions)	Percentage of Scheduled Tribe Population to the total Population
1951			
(a) As per the 1950 Order	19.1	36.1	5.30
(b) As per the 1956 Modification Order.	22.5	36.1	6.23
1961			
As per the 1956 Modification Order.	30.1	43.9	6.87
1971			
(a) As per the 1956 Modification Order supplemented by orders relating to new States/Union Territories.	38.0	54.8	6.94
(b) As per the 1956 Modification Order supplemented by orders relating to new States/Union Territories and as per the Scheduled Castes and Scheduled Tribes Modification Orders (Amendment) Act, 1976.	41.0	54.8	7.50

In 1976, the Government promulgated a Scheduled Castes and Scheduled Tribes Modifications Order (Amendment) Act, 1976, to remove area restrictions in respect of

most of the scheduled tribes, barring a few special cases like the Kurumba of Coorg district of Karnataka. Accordingly, the population of the scheduled tribes was estimated by the Census authority. The estimated population was published in the Government Gazette Notification dated the 20th August, 1977. According to this, the scheduled tribe population was estimated at 41.0 million—an increase of 3 million over the 1971 Census enumeration. This constituted 7.50 per cent of the total population of the country. As expected, the growth of scheduled tribes in the decade 1961-71 varies in the different States/Union Territories, the highest being in Gujarat (35.58 percent and the lowest in Himachal Pradesh (15.76 per cent).

Some Important Issues

From the available information, it is fairly clear that scheduled tribes as a category have been growing at a somewhat higher rate than that in the case of the general population. Therefore, the fear expressed in certain quarters that tribal populations are tending to decline is unfounded. However, it must be recognized that scheduled tribes consist of various communities of different ethnic origins and socio-cultural levels which, among them, have differential rates of growth. While some scheduled tribes have shown pronounced growth rates, others have not shown such a trend. By and large, however, the scheduled tribes which are growing at a fast pace have a large population base and also happen to be well settled agriculturists like the Bhil and the Gond. On the other hand, tribal communities like the Arandan of Kerala and Onges of Andman Islands, etc. which are small are either declining or are not growing fast enough. These are mostly primitive or backward tribes living in isolation as semi-nomads and dependent on food gathering and/or a hunting economy. One wonders whether low rates of growth, area attributable to primitive economy, malnutrition and low fertility of women, caused by inbreeding practised within demographic or cultural considerations and compulsions.

Family planning and family welfare programme will differ from tribe to tribe. Uniform policy will not be desirable. For large tribes growing at a fast pace such as the Gond, the Santhal and the Bhil, the policy need not be different from what is applied to general population. The tribes which are declining or which have registered very low growth rates, a different approach would be called for. In fact, the reasons for low growth need to be identified for appropriate policy measures.

Most of the scheduled tribes are agriculturists and follow rather elementary methods. Most of the minor tribes which are in the pre-farming stage of economy have apparently not received much attention. Effective programmes for their socio-economic development must be evolved. A differential approach would be necessary depending on the size of the tribe, its location and its basic economic and social characteristic.

A differential approach would appear to be necessary in the field of education also. Formal education among scheduled tribes has only just begun. Literacy among the scheduled tribes is still rather low. In this context careful consideration would be necessary about the language in which education and knowledge should be imparted and whether education should be more vocational.

In recent years some tribal communities have come under the direct influence of industrialisation and urbanisation. From Bihar and Orissa a good number of tribals have migrated to industrial, belts as well as to tea estates in Assam and Meghalaya.

Development of tribal communities cannot be an exact replication of the programmes for the general population because here one is dealing with identifiable groups with a common set of socio-economic, ethnic and value systems of their own. Whether one talks of health or education, or progress in totality, it would seem that the content of every programme must be specially attuned to tribal needs. In today's context, the question would be how to bring about economic and social development to the tribal people without economic exploitation, allowing them to retain their social, cultural and ethnic characteristics.

Highlights of Discussions : Session IV

Genetico-Environmental Studies on Indian Tribes : Consideration of Approaches for Promotion of Health Care.

Singh : The definition of tribe should be broad based. Smaller and primitive tribes should be studied more seriously. The tribals of India with low literacy rate are at a low level of agricultural technology. The development plans should be based on their individual needs. The need for indepth investigations on medical, genetic and nutritional profiles can hardly be over emphasised.

Malhotra : The problems of the tribal population groups are manifold. Documented information on the incidence of genetic and other disorders is scanty. Till date, the emphasis has been on cultural aspects and social change among the tribals. Data available on sickling and G-6-PD deficiency are not comparable between one group and another because of differences in methodology and techniques used. However, the picture is far from complete. We must admit that information on other disorders, e. g. nutritional deficiencies, anaemias, etc. is meagre.

Gupta : It would be appropriate to begin with the primitive population groups. Because of geographical location, migration and nomenclature, etc. we do not have any precise information even on the numerical strength of these populations groups. Scarcity of pure drinking water is probably one of the major causes of precipitation of diseases among the tribals. The taboos, are the major impediments against promotion of health measures. Concerted efforts have to be made to raise the tribals from the rut.

Basu : No comprehensive study has been carried out on Indian tribal population groups taking into account both environmental and genetic aspects. The magnitude of the problem calls for multidisciplinary research studies on the tribal population groups.

Gupta : The baseline information on the fertility, mortality and morbidity

patterns among the tribal population groups is essential for planning the developmental programmes.

Bardhan : It is well known that tribals use herbs and plant extracts etc. to ward off disease. For proper delivery of health care among the tribal population groups, study of health culture is important. It may lead to understanding of their needs as well as orientation and approach to be adopted. Information on their perception of disease and their beliefs and taboos, etc. should give proper insight.

Kate : Similarly, the extensive and comprehensive studies on the nutritional content of the traditional foods may provide useful information.

Gupta : The tribal research institutions are in touch with the respective tribal population groups in their areas. Strengthening of Tribal Research Institutes will probably be the optimal approach to obtain useful information. For specialised extensive investigations the Tribal Research Institutes can serve as base laboratories.

Malhotra : Because of the difficult geographical locale, transportation problems, etc. in which the tribals live, I feel more Primary Health Centres should be provided for proper health coverage.

Balaraman : More Primary Health Centres would not help if other infrastructural facilities are not provided. The tribal girls should be trained as nurses and midwives to generate a better response to health care.

Roy : In fact to cover all the factors which have surfaced during discussions experts from various disciplines such as Anthropology, Genetics, Medicine, Botany, Pharmacology, Nutrition and Social Sciences may constitute a team for comprehensive understanding of the problems of tribal population groups.

SESSION V

Genetic Counselling

Keynote Addresses :

Concept and Scope of Genetic Counselling in Indian Context S. S. AGARWAL

Risk Estimates for Genetic Disorders leading to Birth Defects and Mental Retardation-An Indian Perspective L. M. AMBANI

Highlights of Discussions

Concept and Scope of Genetic Counselling in Indian Context

S. S. AGARWAL

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Counselling with respect to the prediction of the risk of occurrence or recurrence of a genetic disease (and its management) has undergone radical changes during the last decade. The role of genetic counsellor has changed from that of a soothesayer to a medical practitioner. (WHO. Tech. Rep. Ser. 416, Bergesma 1970, Hsia etal. 1979, Capron etal. 1979, Epstein etal. 1979, Reed 1980). Along with it goes the tort liability in genetic diagnosis and counselling (Buri and Necht 1982). The recent developments in the field are responsible for this change which includes the following :

There has been increasing recognition of heterogeneity among genetic disorders (Stanbury and Freidrickson 1978, McKusick 1978). Many of the conditions which look alike result from mutations at different gene loci (genocopies), which may not only lead to differences in the course and severity of the diseases but may also be inherited differently. In some instances even an environmentally induced (acquired) disease may mimic a genetic disease (phenocopy). Accurate diagnosis must preceed counselling. Thus, for present day genetic counselling, simple knowledge of mendelian principles of inheritance is not enough. It has to be combined with medical expertise for arriving at the diagnosis of the genetic disorders.

Many of the genetic disorders, if diagnosed in time and managed properly, may now be compatible with normal life and even fertility (Holtzman 1970, Rosenberg 1976). Therefore, while counselling for the risk of occurrence and possible options, one has to carefully weigh the options of non-procreation vs. adequate manage-

ment. Also, since the counsellee often has an affected child or a near relative, the counselling center needs to be equipped with proper medical care facilities.

All the chromosomal abnormalities and a large number of inborn errors of metabolism can now be successfully diagnosed in utero (Milunsky 1979 and Milunsky 1981) and as a result counselling practice has undergone tremendous changes. Prior to these developments a counsellor could not go beyond predicting the probable risk. Now it can be accurately determined in a number of instances, whether the given foetus is affected or not. Coupled with this advancement the legal sanction of medical termination of pregnancy, can ensure the prevention of the birth of an affected child. Antenatal diagnosis of genetic disorders has become an integral component of genetic counselling, wherever possible, especially in case of neural tube defects etc.

So far genetic counselling has been usually sought by the couples who have an affected child. Thus, the advice is given after the occurence of at least one event. It may be important for the family to prevent the recurrence, but the deleterious genes remaining in the population continue to burden the society with the affected children. The problem can be mitigated by the screening of heterozygotes in the population and counselling before contemplation of marriage (marriage counselling)or birth of first child. This concept has been successfully employed for Tay-Sachs disease which could be a fore-runner for others (Kaback 1973). Screening of heterozytoges in the population is one of the most radical concepts in preventive medicine.

The success in preventing mental retardation in phenylketonuric child by eliminating phenylalanine from the diet of a neonate has led to the emergence of the concept of national screening for inborn errors of metabolism (Levy 1975). The cost-benefit analysis has established the utility of many of these screening programmes which have been made mandatory by legislation in several states in the United States. (Reiley 1975.) This has added a new dimension to the genetic counselling programme which deals with the mitigation of suffering due to genetic disorders. With respect to counselling for management of genetic disorders, the concept of genetic engineering has already taken practical shape. It requires no crystal gazing to predict that the future of genetic counselling is bright.

Genetic counselling is a therapeutic measure. It includes establishment of an accurate diagnosis, treatment of the affected individual as well as the prevention of the reccurrence of genetic disorder. A very important role that a genetic counsellor can play is of allaying fears borne out of ignorance. Genetic counselling requires a special aptitude in the art of communication. Genetic counselling must be non-directive while the

information, shall be complete, accurate and comprehensible to a lay man, The counsellor shall excercise his or her judgement regarding the best possible manner in which the advice is to be given to the counsellee. The advice shall include information about the potential medical, social, economical and psychological burdens on the one hand and various reproductive options and alternatives available to the counsellee on the other hand. The final decision shall rest with the consultands.

With reference to Indian situation, the priorities and extent of development of services are open to adjustments according to national needs. The problems of nutrition, infection and population control are so pressing that everything else seems to be of less importance. India is a large country and in absolute terms even the rare disorders assume sizeable proportion. For example, the incidence of chromosomal abnormalities, which is 0.5 per cent of all live births, approximately, 120,000 affected children may be born with chromosomal anomalies every year in the country. The second example is that of rare monogenic disorders. Taking an extreme case of rarity, with an average incidence of 1 in 50,000, approximately 480 children may be born in the country. Though this number is not large, it cannot certainly be ignored. In coming years, with the control of environmentally induced diseases, the importance of genetic disorders is bound to increase.

Further, the problem shall not be viewed only in terms of numbers. For one who suffers, even the single case of a disease is as vital as any other common disease. Moreover, the national loss in terms of man years lost in productivity on the one hand and the costs of intensive or custodian care of handicapped child on the other hand, may even be larger than that spent on many common diseases (Stickle 1965). In addition, the national need for limiting the family size puts a heavy premimum on the state to ensure that all those who are born are free from physical and mental handicap as far as possible (Roy and Ghosh 1972). Thus even in Indian context, there can be no doubt about the importance of genetic diseases. It is necessary that regional centres well equipped with comprehensive diagnostic and therapeutic facilities should be established to provide care and prevention of genetic diseases.

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Risk Estimates for Genetic Disorders Leading to Birth Defects and Mental Retardation : An Indian Perspective

L. M. AMBANI

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What is Genetic Counselling

Genetic Counselling is the process of communication between the parents of a child affected with a genetic condition and the counsellor who conveys information regarding the prognosis and the available modes of therapy for the proband as well as risks of recurrence and methods of prevention of affected future children.

Need for Genetic Counselling in India

Genetic Counselling is required by the poor and the rich alike. Of course, the precise way in which genetic counselling is given must be tailored according to the socio-economic and educational background of the parents. At the Institute for Research in Reproduction, we have found the response equally encouraging from parents of different backgrounds.

Team work for Genetic Counselling

Genetic counselling requires a team work for being ideal. However, a general practitioner can provide genetic counselling in straightforward cases. Since an accurate diagnosis is important, a medical geneticist is the ideal person for complex cases. A social worker is of great help in genetic counselling.

Cases for Genetic Counselling

Invariably the parents of children with mental retardation, congenital malformation(s), abnormal sex differentiation, short stature, clinical conditions due to single gene mutations, e.g., hemophillia, thalassaemia, duchenne muscular dystrophy, couples with consanguinity (premarital genetic counselling), recurrent abortion and infertility seek genetic counselling.

Some Principles of Genetic Counselling

Both parents should be counselled together as far as possible. Care must be taken to see that 'blame' is not put on one of them.

Only preliminary genetic couse!ling should be given during the period immediately following birth of a defective child. Detailed genetic counselling must be undertaken later when initial reactions of grief, denial, guilt, blame, etc., have worn off.

Follow-up session is always desirable even in other cases to assess the accuracy and degree of understanding during genetic counselling. Further developments in clinical and laboratory aspects may allow for a better diagnosis.

One should not paint a very grim picture. It is best to be realistic but not pessimistic. We must recognize wide variations in development, e.g., of a Down's syndrome child.

Successful Genetic Counselling

The following are the essential prerequisits for successful genetic counselling.

Accurate diagnosis of the condition.

Awareness of the principles of mendelian inheritance and polygenic traits.

Aptitude to look for new syndromes.

Ability of counsellor to tailor according to the couple's background.

Attentive and motivated "Consultand parents".

Appropriate timing of the counselling.

Empathy for the Consultands.

Accurate Diagnosis of the Condition

It is very important to establish a proper diagnosis of the cause for which the patient is referred for counselling. The accurate diagnosis is half the battle won. This

is particularly important in conditions such as mental retardation, congenital malformations, ambiguous genitalia and infertility in which there can be both genetic and environmental causes operating. Again, there can be several types of genetic disorders leading to a similar phenotype. For an accurate diagnosis one needs the following :

Clinical expertise : What the mind does not know, the eyes do not see. The counsellor should be well versed with the literature on the disorders for which his advice is sought for. He must be aware of the various differential diagnostic possibilities. He should take a thorough history, perform an extensive and complete physical examination and then select the various laboratory tests required to come to a specific diagnosis. For children with mental retardation and/or birth defects, the clinical examination can provide, many a time, interesting clues to the diagnosis. For example, an indented ear lobule in a large baby (Beckwith Wiedemann syndrome), polydactyly, obesity and hypogonadism (LMBS Syndrome), Cafe-au-lait spots (neurofibromatosis), etc. He should have an easy accessibility to reference books, e.g., Mckusick's catalogue, Warkany's book on 'Congenital Malformations, etc. This is very essential because each of the genetic disorders leading to mental retardation and birth defects is by itself very rare.

Biochemical laboratory back-up : A battery of simple biochemical tests such as $FeCl_3$, DNPH, Nitroprusside, acid albumin test, etc., chromatography for amino acid, organic acids, etc., can be applied to all patients whereas selective use of specialised tests such as plasma ammonia, specific enzyme levels, quantitative determination of plasma amino acids or organic acids (on GLC or HPLC) need to be performed on some of the patients to arrive at a specific diagnosis. In India, we need not only to standardise the various tests but also to perform them on enough number of controls to get data for our populations.

Cytogenetic investigations : Chromosomal studies are required in patients with congenital malformations with or without mental retardation, particularly when one cannot diagnose a specific monogenic or environmental syndrome or when one suspects a particular chromosomal abnormality such as Down's Syndrome to confirm the diagnosis. For patients suspected to have a small structural abnormality of the chromosomes, one should perform not only regular G-banding but also carry out high resolution C and/or R banding studies. Some patients may require study of sister chromatid exchanges (SCEs), or of chromosomal breaks and gaps. Further, studies on different tissues may be required.

Availablity of consultation with other specialists and facilities for other investigations such as radiological, clinical, pathological and hormonal studies : The consultants most often helpful in arriving at an accurate diagnosis are the radiologist opthalmologist, neurosychiatrist, dermatologist and cardiologist.

Follow-up visits : Very often, the precise diagnosis can be established only at subsequent examinations. This is particularly true for some of the syndromes leading to mental retardation. We have often diagnosed a specific syndrome only at the second or third visit of the patients.

Awareness of Principles of Mendelian Inheritance

A counsellor should have a thorough knowledge of the principles of Mendelian inheritance as well as those governing the multifactorial traits. A detailed pedigree should be drawn for each case, particularly, where the diagnosis of the chromosomal syndrome is not obvious. For the latter group, if another family member is similarly affected, it may help uncover those 'at high risk' in such families and to define the exact translocation or other chromosomal abnormalities in such individuals. The counsellor should be able to understand not only the principles governing the patterns but also be able to apply them to individual families and to convey the information so obtained in a language that the counsellee can understand.

AD traits : For suspected or known autosomal dominant traits, a very careful examination of the apparently unaffected members should be done to determine the partial expressivity of the condition. For some conditions such as Achondroplasia, if the parents are normal, the recurrence risk is nearly zero percent, since the patient represents a new mutation. However, care is to be exercised not to lump every short-limbed dwarf as an Achondroplast. For example, Achondrogenesis, an autosomal recessive trait, should be ruled out by proper radiological examinations. In a condition such as Neuro-fibromatosis, one should look for iris nodules as a possible marker of the abnormal gene or phakoma in cases of Tuberous Sclerosis.

AR traits : In autosomal recessive traits, history of consanguinity is often found. However, one must remember that absence of consanguinity does not rule out carrier status in the parents for conditions such as PKU, Homocystinuria, etc., which are known to be inherited. On the contrary, the presence of consanguinity alone does not mean that a disease is inherited as a recessive trait.

X linked recessive traits : A patient with X-linked recessive trait may have a history of brother, maternal uncles or maternal male cousin having been affected. For example, in a family with Hunter's syndrome, at first, we were told by the family that no one was affected. However, on close enquiry, we could obtain photograph of a maternal uncle who had died during childhood and looked obviously a case of Type II Mucopolysaccharidosis. In X linked recessive disorders in which the son is the first affected, the mother's carrier status must be determined by some biochemical test. This is possible in DMC, Hemophilia, Hunter's disease, etc. The risk of recurrence, if mother

is found to be a carrier is 50 per cent to each of her male children, whereas if she is not, the risk is negligible. In X linked recessive traits, if the female is affected, we must consider the possibility of her being homozygous (a product of a carrier mother and an affected father), Turner syndrome with a single X (and hence homozygous) or lyonization favouring preferential inactivation of the X chromosome carrying the normal gene.

X linked dominant traits : What may appear initially to be inherited as an antosomal dominant trait may be found on closer scrurtiny to be an X linked dominant trait. On analysis of a large pedigree, a female to male ratio of two and an absence of male to male transmission, help in considering the diagnosis of an X linked dominant trait. In a condition such as hypophosphatemic rickets, low phosphorus level in unaffected families allowed the diagnosis of X linked dominant pattern of inheritance. In OTC deficiency, only females were initially found to be affected. However, on detailed pedigree analysis, it was obvious that the males being more severely affected had died during early newborn period and that was the cause of absence of living affected male children in the families.

Multifactorial or polygenic traits : Many common disorders affecting large number of people in the population are due to genetic and environmental factors operating together. These are called multifactorial traits. The recurrence risk is usually determined, empirically, based on the observed family data. This type of data are practically non-existent in India. The polygenic conditions for which these risk estimates are required to be established are (i) congenital heart disease, e.g., VSD, ASD, PDA, TOF, etc.; (ii) neural tube defects such as anencephaly, spina bifida, hydrocephalus, etc.; (iii) pyloric stenosis; (iv) schizophrenia; and (v) club foot, etc. For some conditions, such as cleft lip/cleft palate some data have been collected.

In spite of the paucity of the exact percentage recurrence risk, one can counsel the families properly if the following aspects of these traits are remembered.

The usual risk of recurrence varies from 2 to 5 percent and represents a to 40 square root of the frequency of the condition in the general population. This is 20 times the general frequency within the population groups.

The risk increases about two to three fold with every extra sib affected and/or one parent affected.

The more severe the malformations, the greater is the recurrence risk.

The risks are often influenced by sex of the proband. Susceptibility of the individuals often varies according to the sex.

Aptitude to Look for New Syndromes

Very often, the counsellor is faced with a set of symptoms and signs which do not fit into any known syndrome and in which the malformations are not due to any chromosomal or biochemical abnormalities. In these cases, good pedigree data collected by extensive and exhaustive interview of the patients and their relatives are required for the purpose of such a diagnosis. In several instances we were able to identify a unique mode of inheritance. Some examples are given below :

ACPS-II is normally supposed to be inherited as an autosomal recessive trait. We found evidence of its being transmitted as a dominant trait in a four generation pedigree affecting several paternal relatives to a variable degree, but affecting none of the maternal relatives.

Hydatidiform mole is generally considered to be a polygenic condition. In three families, two or more sisters had one or more molar pregnancies. A study of these families suggested that a genetic factor transmitted through females might be the cause of recurrent moles in at least some families. The basic defect, we postulated, could be in the ovum which allows loss of mother's own set of chromosomes and duplication of father's chromosomes.

Hirschsprung's disease and Waardenburg's syndrome were found in multiple siblings in five families. Waardenburg's syndrome itself is inherited as an antosomal dominant trait whereas Hirschsprung's disease is a polygenic condition. A detailed history and a careful examination of many relatives allowed us to postulate that this is a new syndrome with autosomal recessive pattern of inheritance.

Pyknodysostosis is considered to be inherited as an autosomal recessive trait. We had one family data consistent with an autosomal dominant form of inheritance.

Ability of Counsellor to Tailor According to the Couple's Background

The counsellor must take into account the needs of the patient. He should convey the information in simple terms. Many of the patients expect the doctor to tell them what would he do under the circumstances. If the risk is higher than 10 per cent or even if the risk is about 2 to 5 percent, the economic burden imposed by the recurrence is high, and if the prenatal diagnosis or treatment for the condition is not available, the parent should be advised not to undertake any further pregnancy. The decision should be left to the parents. If properly informed, we have found that even uneducated couples often do not undertake further child-bearing if there is a high risk of recurrence.

Attentive and Motivated Consultand Parents

It is essential that the parents should have motivation to seek advice and informa-

tion regarding the prognosis for the proband and the risk of recurrence. Down's syndrome is the commonest genetic cause of mental retardation. It causes a lot of anxiety in the parents and although the risk of recurrence is only 1 to 2 percent most of the parents, irrespective of their socio-economic background, do wish to prevent the risk of affected child.

Appropriate Timing of the Counselling

The birth of a defective child imposes a mental burden on the parents and causes grief, guilt and blame or even denial. At such a time, it is best to have only a brief session and leave the remaining discussion to a subsequent visit. The denial is particularly common in cases of Down's syndrome or other metabolic disorders when diagnosed at an early age, since the child does not look much different from a normal one. Only when the child grows and starts lagging behind, do the parents accept that the child is indeed abnormal or retarded. It is, therefore, best to inform the parents during the initial visit of the possibility of a subsequent lag in development. One should not, however, convey a very pessimistic view since there is a lot of variation in the degree of mental retardation in Down's syndrome. It is best to follow-up regularly the growth of his or her brain and motor development at 6 to 12 months intervals. During subsequent visits, one can determine the growth potential of such children. For young couples, the information regarding prenatal diagnosis and its availability should be conveyed as soon as the diagnosis is confirmed.

Empathy for the Consultands

Last but not the least, the success of a genetic counselling session depends on the rapport established with the couple by the geneticist who should be able to convey a sense of involvement in the problems of the parents and the child.

Highlights of Discussion : Session V

Genetic Counselling

Roy : The two preceding addresses make it clear that there is tremendous scope for genetic counselling in India. Concerted efforts are required to generate data on the incidence of congenital malformations and empirical risks estimates for effective genetic counselling. To expedite establishment of genetic counselling services, regional approach for collection of the data through prospective and retrospective studies should be adopted.

Agarwal : Low ratios of the disease should not deter us from developing the genetic counselling services in India.

Malhotra : Human suffering cannot be quantified in numbers. The need for genetic counselling cannot be set aside because of lack of resources and utility.

Ambani : Reports on congenital disorders are sporadic. Accurate diagnosis of the genetic disorders is one of the major issues. Because of lack of orientation of medical doctors to the genetic disorders, many rare disorders may go unnoticed. Organisation of the training courses and orientation camps, inclusion of medical genetics and human genetics in the curriculum at undergraduate level are essential steps in this direction.

Sukumaran : The baseline data on the incidence of hereditary disorders congenital malformations are lacking. Some information is available on the prevalence of haemoglobinopathies in some areas. Efforts should be made to generate strong base-line data, an essential pre-requisite for genetic counselling.

Grewal : Possibly the screening of hospital patients as well as population groups can be simultaneously undertaken.

Ambani : Such data are of utmost importance in deriving the recurrence risk estimates among the population groups.

Veerraju : Polygenic and multifactorial disorders should be given more emphasis since these may be more frequent in the population groups.

Marimuthu : Due cognizance should be given to socio-biological correlates and their effects on the incidence of various genetic and genetico-environmental disorders.

Balaraman : For the establishment of genetic counselling services, infrastructural facilities in terms of trained manpower, necessary equipment, etc. should be considered. Regional genetic counselling centres with properly trained manpower, equipment and other infrastructural facilities may be a feasible approach.

Basu : The frequency of different genetic disorders varies in different population groups. Counselling at community level, may be through imparting genetic knowledge, will evoke a better response from the group.

Malhotra : It would be worthwhile to establish a central genetic registry to obtain national figures for various genetic disorders in the country.

Bardhan : Along with the central registry, a central data bank and clearing house should be created for dissemination of information on various disorders in the Indian population groups.

SESSION VI

Priority Areas and Centres for Collaborative Research in Human Population Genetics for Promotion of Health Care

Highlights of Discussions : Session VI

Priority Areas and Centres for Collaborative Research in Human Population Genetics for Promotion of Health Care

Kalla : The priority research areas can be perceived either in terms of size and growth rates of population groups or in terms of their health characteristics. The small population groups showing high frequency of disorders, e.g. haemoglobinopathies, G-6-PD deficiency, etc. should be investigated in details and preventive and promotive aspects of health care should be promulgated.

Baxi : While the populations should be screened for priority problems like haemoglobinopathies and G-6-PD deficiency, study of genetic markers like blood groups, serum poteins and enzyme polymorphisms may be inducted in the screeing programme from population genetic point of view. Attempts should be made simultaneously to elicit the genetic markers and disease associations.

Roy : Induction of socio-economic and other socio-biological correlates affecting the susceptibility to disease may increase the value and utility of the data. While studying the disease component in relation to genetic markers, multigene marker approach followed by a multivariate analysis should be adopted to yield data which can be effectively utilized in identification of high risk groups.

Basu : Besides the scheduled tribes and castes, there are many groups which have not been identified because of problems of nomenclature, etc. These groups face the prospect of extinction. Identification of these groups and study of their socio-biological and genetic attributes should be given priority.

Agarwal : Three basic principles determine priorities. We know the high frequency of various abnormal haemoglobins, G-6-PD deficiency and other disorders among the tribal population groups. We should first begin with strengthening the

preventive and promotive aspects of health care among them on priority. Secondly, since the problems are multifaceted and multidimensional in nature, multicentric and multidisciplinary co-ordinated approach should be adopted. Finally, the requirements may be conceived from three different aspects, i.e. felt need, scientific need and thought need. The first refers to the demands of the population group, the second refers to what action ought to be initiated scientifically either for basic research or applied, curative, preventive and promotive aspects. The third singnifies what quality of life should be in terms of minimum health status.

Bhalla : The frequency of disorders like G-6-PD deficiency is very high in some non-tribal population groups also. It seems desirable to make comparisons on the basis of gene pool.

Agarwal : We do not have complete information on the caste, sub caste and clan structure to understand the extent of genetic hetrogeneity of the population groups which may have influence on the results and projections thereof. Multigene marker studies can be extended to establish genetic identity of the population groups. Occurrence of high frequency of inbreeding and its effects on the fertility, mortality calls for further indepth investigations. Investigations on genetic markers are needed to develop them as diagnostic tools.

Roy : Till now, the investigations have been mainly to find out the occurrence of various genetic disorders in the population groups. Concerted efforts have not been made to study the health hazards due to these genetic disorders. Attempts to evaluate these genetic disorders and their variable manifestations in terms of clinical severity and long term and short term preventive, promotive and prognostic measures are needed.

Reddy : Newborn screening should be undertaken on priority for genetic disorders for which intervention measures are possible.

Roy : Screening may help in early diagnosis of galactosamia, phenylketenuria and other disorders which lead to mental disabilities and where some interventions are possible. As far as antenatal diagnosis is concerned, it is a specialised job for which hospitals will have to take up the responsibility.

Das : No doubt the tribal population groups should be given priority but there are other backward population groups with similar problems. Instead of limiting the scope to tribals, it should be extended to non-tribal, backward population groups. Researches on the prevalence of infectious diseases should be given priority on the basis of their relative incidence in different regions and areas of the country.

Singh : Population isolates inhabiting the hostile geoclimatic terrains in the

country should receive priority because of the genetic and genetico-environmental disorders prevalent among them. Multiple gene marker studies incorporating their socio-biological correlates should be undertaken. The heirarchial caste system, endogamy and inbreeding should be viewed in a broader perspective in Northern and North Eastern region. Concerted efforts are needed to resolve the genetic heterogeneity of the Indian population groups. Lastly, the preventive and promotive health care should be strengthened among the decling population groups.

Tiwari : Those populations which have shown a high incidence of genetic disorders should be extensively studied and genetic maps may be prepared. Comprehensive medical care including preventive and promotive health care should be provided to those populations where genetic disorders pose significant problems. Second priority should be to study the unexplored population groups.

Swarup-Mitra : How can we ignore the need to provide for preventive and promotive health care in population groups with genetic disorders for which data are not presently available?

Roy : One of the major lacunae in the available information is that coverage is not uniform. It is envisaged that a beginning can be made in populations and areas where information is available and in any case we do not intend to neglect where the information is not available.

However, I wish to introduce the next part of the theme of the session, i.e. identification of research centres.

Agarwal : Dr. I.C. Verma has already prepared a directory of the various research centres which are actively engaged in research on various aspects of population genetics.

Baxi : It needs updating and revision with respect to fast developments in various centres.

Ambani : Under the auspicies of Indian Society of Human Genetics, Dr. V. Balakrishnan has already initiated the preparation of a registry of human population geneticists in India. A collaborative effort may help in the preparation of a comprehensive catalogue.

Das : The most important aspect from practical point of view is the co-ordination of activities which can best be achieved by creating a task force on 'Population Genetics and Health Care' which should act as a guiding, advisory and co-ordinating body. The recommendations of this workshop can easily be transformed into the tenets of this body.

Singh : This advisory body can provide guidance for effective implementation of the recommendations of this workshop. Beside that, this body can initiate activities like organising workshops, study groups etc. for standardisation of methodology, organisation of training courses at the universities, and can monitor quality control of researches done within the country.

Roy : A co-ordinating body is essential to look into standardisation of methodology and give proper direction to the researches in human population genetics.

Dubey : The basic functions of a task force are promotion of quality, standardise the methodological approach and organise the training courses and workshops, etc. The urgency of the problems, nature of problems which are multidisciplinary and the information which need to be gathered for augmenting preventive and promotive health care are justifiable enough to interest any funding agency.

Roy : The need of the hour is the development of suitable standardised methodological approach for researches in human population genetics and it is to be ensured that reseachers use these methodologies.

A. Basu : Effective implementation of the recommendations of the workshop can yield much needed information towards evolving an effective preventive and promotive health care for the country.

Agarwal : National Institute of Health & Family Welfare, having already taken the initiative in the organisation of the workshop of this nature, would be better suited to evolve the plan of action for implementing the recommendations of the workshop.

Annexures

Organisation

Workshop Director	**Prof. Somnath Roy** Director, National Institute of Health and Family Welfare New Delhi
Workshop Co-Ordinator	**Dr. S. K. Basu** Head, Department of Population Genetics and Human Development, National Institute of Health and Family Welfare New Delhi.

Planning Group

1	*Prof. Somnath Roy* Director, National Institute of Health and Family Welfare, New Delhi.	Chairman
2	*Prof. I.P. Singh* Head, Department of Anthropology, Delhi University, Delhi.	Member
3	*Dr. S.C. Tiwari* Department of Anthropology, Delhi University, Delhi.	Member
4	*Dr. M.S. Grewal* Department of Anatomy All India Institute of Medical Sciences, Ansari Nagar, New Delhi.	Member
5	*Dr. S.K. Basu* Head, Department of Population Genetics and Human Development, National Institute of Health and Family Welfare, New Delhi.	Member-Secretary

Programme

MARCH 24, 1982

Inaugural Session

0930-1000 hrs.	Registration
1000-1030 hrs.	Welcome Address *Prof. Somnath Roy* Director, National Institute of Health and Family Welfare, New Delhi.
1030-1100 hrs.	Inaugural Address *Prof. H.D. Tandon* Director, All India Institute of Medical Sciences, New Delhi
1100-1115 hrs.	Vote of Thanks *Dr. S.K. Basu* Head, Department of Population Genetics and Human Development, National Institute of Health and Family Welfare, New Delhi.
1115-1130 hrs.	*COFFEE BREAK*

Session-I

Haemoglobinopathies and Allied Disorders in india-Genetic Implications and Importance in Health Care

Chairperson : *Prof. Somnath Roy*
Rapporteurs : *Dr. Anil Jindal*
Dr. G.K. Kshatriya

1130-1200 hrs. Abnormal Haemoglobins in India : A Critical Appraisal with Particular Reference to Promotion of Health.
Dr. P.K. Sukumaran

1200-1230 hrs. Glucose-6-Phosphate Dehydrogenase Enzyme Deficiency in India : Prevalance and Public Health Implications.
Dr. A.J. Baxi

1230-1300 hrs. Clarifications and Discussions

1300-1400 hrs. *LUNCH BREAK*

1400-1430 hrs. Group Discussion and Formulation of Observations and Recommendations.

Group-I

Chairperson : *Dr. S. Swarup-Mitra*

Rapporteurs : *Dr. S.L. Kate*
Dr. Anil Jindal

Group-II

Chairperson : *Prof. K.M. Marimuthu*

Rapporteurs : *Dr. P. Veerraju*
Dr. G.K. Kshatriya

MARCH 25,1982

0930-1030 hrs. Presentation and Adoption of Observations and Recommendations of Session I

Chairperson : *Dr. K. Balaraman*

Rapporteurs : *Dr. Anil Jindal*
Dr. G.K. Kshatriya

Session-II

Association of Genetic Markers with Health and Diseases.

Chairperson : *Dr. S.S. Agarwal*

Rapporteurs : *Dr. Anil Jindal*
Dr. G.K. Kshatriya

1030-1100 hrs.	Blood Group and their Association with Diseases : *Dr. S.C. Tiwari*
1100-1115 hrs.	*COFFEE BREAK*
1115-1145 hrs.	HLA Antigens and Diseases : A Review *Dr. N.K. Mehra*
1145-1415 hrs.	Clarifications and Discussions

Session-III

Inbreeding in India : Its Genetic Consequences and Implications in Health Care *Dr. S. K. Basu*

1215-1245 hrs.	Inbreeding in India : Its Genetic Consequences and Implications in Health Care *Dr. S.K. Basu*
1245-1300 hrs.	Clarifications and Discussions
1300-1400 hrs.	*LUNCH BREAK*
1400-1630 hrs.	Group Discussion and Formulation of Observations and Recommendations for Sessions II and III.

Group-I

Chairperson : *Prof. B. M. Das*

Rapporteurs : *Dr. V. Bhalla*
Dr. Anil Jindal

Group-II

Chairperson : *Dr. M.S. Grewal*

Rapporteurs : *Dr. Y.R. Ahuja*
Dr. G.K. Kshatriya

MARCH 26, 1982

0900-1000 hrs. Presentation and Adoption of Observations and Recommendations of Sessions II and III.

Chairperson : *Dr. S.S. Agarwal*

Rapporteurs : *Dr. Anil Jindal*
Dr. G.K. Kshatriya

Session-IV

Genetico-Environmental Studies on Indian Tribes : Consideration Of Approaches For Promotion of Health Care.

Chairperson : *Dr. Bhupinder Singh*

Rapporterus : *Dr. Anil Jindal*
Dr. G.K. Kshatriya

1000-1025 hrs. Medico-Genetic Problems of the Tribal Communities of India *Prof. I.P. Singh*

1025-1050 hrs. Population Trends among the Tribal Groups of India *Shri P. Padmanabha*

1050-1120 hrs. Clarifications and Discussions.

1120-1130 hrs. *COFFEE BREAK*

Session-V

Genetic Counselling

Chairperson : *Prof. K.M. Marimuthu*

Rapporteurs : *Dr. Anil Jindal*
Dr. G.K. Kshatriya

1130-1155 hrs. Concept and Scope of Genetic Counselling in the Indian Context *Dr. S.S. Agarwal*

1155-1220 hrs. Risk Estimates for Genetic Disorders Leading to Birth Defects and Mental Retardation - An Indian Perspective.
Dr. L. M. Ambani

1220-1300 hrs. Clarifications and Discussions.

1300-1400 hrs. *LUNCH BREAK*

1400-1630 hrs. Group Discussion and Formulation of Observations and Recommendations for the Sessions IV and V.

Group-I

Chairperson : *Dr. K.C. Malhotra*

Rapporteurs : *Dr. P.K. Ghosh*
Dr. Anil Jindal

Group-II

Chairperson : *Prof. I.P. Singh*

Rapporteurs : *Dr. A. Basu*
Dr. G.K. Kshatriya

MARCH 27, 1982

0930-1030 hrs. Presentation and Adoption of Observations and Recommendations of Sessions IV and V.

Chairperson : *Prof. I.P. Singh*

Rapporteurs : *Dr. Anil Jindal*
: *Dr. G.K. Kshatriya*

1030-1050 hrs. *COFFEE BREAK*

Session-VI

Priority Areas of Research in Human Population Genetics : Identification of Centres for Collaborative Research for Promotion of Health Care.

Chairperson : *Prof. Somnath Roy*

Rapporteurs : *Dr. P.K. Sukumaran*
Dr. Anil Jindal

1050-1300 hrs,	Group Discussions and Formulation of Observations and Recommendations and Adoption of Observations & Recommendations of the Session VI.
1300-1400 hrs.	*LUNCH BREAK*

Valedictory Function

1500-1615 hrs.	Welcome	*Prof. Somnath Roy*
	Overview of the Workshop	*Dr. S.K. Basu*
	Presentation of Observation and Recommendations of the Workshop	*Dr. P.K. Sukumaran*
	Remarks of the Participants	*Prof. K.M. Marimuthu*
	Valedictory Address	*Col. B.L. Raina*
	Vote of thanks	*Dr. S.K. Basu*

Participants of the Workshop

1	Dr. Arvind J. Baxi	Blood Group Reference Centre, Parel, Bombay
2	Dr. P.K. Sukumaran	Cancer Research Institute, Parel, Bombay.
3	Dr. L.M. Ambani	Medical Genetics Unit, Institute of Research in Reproduction, Bombay
4	Dr. S.L. Kate	Genetics Division, B.J. Medical College, Pune
5	Prof. K.M. Marimuthu	Department of Genetics, Post Graduate Institute of Basic Medical Sciences, Taramani, Madras
6	Dr. M.A. Reddy	Biochemistry Division, Institute of Genetics and Hospital of Genetic Diseases, Hyderabad
7	Dr. Y.R. Ahuja	Department of Genetics, Osmania University, Hyderabad
8	Dr. P. Veerraju	Department of Human Genetics and Physical Anthropology, Waltair
9	Dr. K.C. Malhotra	Department of Anthropology and Human Genetics, Indian Statistical Institute, Calcutta
10	Dr. S. Swarup-Mitra	ICMR Hematology Unit, Calcutta School of Tropical Medicine, Calcutta
11	Prof. B.M. Das	Department of Anthropology, Gauhati University, Gauhati
12	Dr. P. Das Sharma	Department of Anthropology, Ranchi University, Ranchi
13	Dr. A. Basu	Department of Anthropology and Human Genetics, Indian Statistical Institute, Calcutta
14	Dr. R.S. Negi	National Museum of Man, Bhopal

15	Dr. S.S. Agarwal	Department of Medicine, Genetics Division K. G. Medical College, Lucknow
16	Dr. V. Bhalla	Department of Anthropology, Punjab University, Chandigarh
17	Dr. I.J.S. Bansal	Department of Human Biology, Punjabi University, Patiala
18	Dr. L.S. Sidhu	Department of Human Biology, Punjabi University, Patiala
19	Dr. K. Balaraman	Director Health Services, Kerala
20	Sh. B.N. Bordohi	Director Tribal Research Institute, Gauhati
21	Sh. B.B. Nigam	Tribal Research Institute, U.P.
22	Sh. C.R. Nath	Under Secretary, Department of Tribal Welfare, Assam
23	Sh. S.P. Gupta	Director, Tribal Welfare Research Institute, Ranchi
24	Prof. J.R. Bhatia	New Delhi
25	Dr. M.S. Grewal	Department of Anatomy, All India Institute of Medical Sciences, New Delhi
26	Dr. N.K. Mehra	Department of Anatomy, All India Institute of Medical Sciences, New Delhi
27	Dr. I.C. Verma	Genetics Unit, Department of Paediatrics, All India Institute of Medical Sciences, New Delhi
28	Dr. Bhupinder Singh	Joint Secretary, Ministry of Home Affairs, Govt. of India, New Delhi
29	Sh. P. Padmanabha	Registrar General and Census Commissioner Govt. of India, New Delhi
30	Dr. (Mrs.) N. Natrajan	Director (Research), Commission for Scheduled Caste and Scheduled Tribe, Loknayak Bhavan, New Delhi
31	Prof. I.P. Singh	Department of Anthropology, Delhi University, Delhi

32	Dr. S.C. Tiwari	Department of Anthropology, Delhi University, Delhi
33	Dr. P.K. Ghosh	Department of Anthropology, Delhi University, Delhi
34	Prof. H. Walter	University of Bremen, Federal Republic of Germany, Visiting Professor, Department of Anthropology, Delhi University, Delhi
35	Dr. (Mrs.) S. Seth	Department of Anthropology, Delhi University, Delhi
36	Dr. A.K. Kalla	Department of Anthropology, Delhi University, Delhi
37	Dr. P.K. Datta	Department of Anthropology, Delhi University, Delhi.

National Institute of Health and Family Welfare :

38	Prof. Somnath Roy	Director
39	Prof. J.P. Gupta	Joint Director
40	Prof. D.C. Dubey	Department of Social Sciences
41	Prof. S. Bhatnagar	Department of Community Health Administration
42	Prof. P.P. Talwar	Department of Demography and Statistics
43	Dr. (Miss) A. Bardhan	Department of Social Sciences
44	Dr. (Mrs.) S. Sood	Department of Reproductive Biomedicine
45	Sh. B.B.L. Sharma	Department of Demography and Statistics
46	Dr. S.K. Basu	Department of Population Genetics and Human Development
47	Dr. Anil Jindal	Department of Population Genetics and Human Development
48	Dr. (Mrs.) N. Makol	Department of Population Genetics and Human Development
49	Dr. G.K. Kshatriya	Department of Population Genetics and Human Development

Welcome Address

PROF. SOMNATH ROY

Director, National Institute of Health and Family Welfare,
New Mehrauli Road, Munirka, New Delhi-110067

Professor Tandon, Distinguished Participants, Invited Guests, Colleagues and Friends

It gives me great pleasure to welcome you all to this workshop on "Population Genetics and Health Care." To those of you who have come from outside Delhi, and particularly those coming for the first time to this new campus of the National Institute of Health and Family Welfare (NIHFW), I would like to extend our heartiest greetings on behalf of the faculty and staff of the Institute.

As you may be aware that this Institute came into existence following the amalgamation of two erstwhile national institutions, i.e. National Institute of Health Administration and Education (NIHAE) and the National Institute of Family Planning (NIFP), on March 9, 1977. The NIHFW serves as the apex technical institute for promotion of the Health and Family Welfare Programme in the country through education, training, research, evaluation and consultancy services.

To Professor H.D. Tandon, Director, All India Institute of Medical Sciences, we are specially grateful for having readily agreed to our request to address the participants in this Inaugural Session, in spite of his pre-occupations and busy schedule. Professor Tandon is an eminent pathologist whose contributions particularly in the field of gastro-intestinal pathology are nationally and internationally recognized. He has served as an expert and advisor to various national and international committees and organizations. He is a recipient of many prestieous awards and is associated with various scientific and academic bodies.

While welcoming you all to this workshop today, I get a nostalgic feeling as I recall that the very first Workshop on "Medical and Human Population Genetics" in the country was organized at the Central Family Planning Institute, the fore-runner of the National Institute of Family Planning in March, 1967, exactly 15 years ago. The participants to that Workshop included among others, Prof. P.C. Biswas, Prof. S.S. Sarkar, Dr. L.D. Sanghvi, Prof. I. P. Singh and Dr. S. C. Tiwari. In the introductory note to the proceedings of that workshop, the Director of the Institute Lieut. Colonel B.L. Raina, who is a great visionary, stated this workshop, the first of its kind in India, is being organized at the Central Family Planning Institute to review the work carried out in the country and to provide opportunities to the investigators in this field for exchange of views on various problems. Scientists from different parts of the country and belonging to diverse disciplines discussed various aspects of cytogenetics, medical genetics including genetic counselling, genetic hazards of radiation, and the work done on population genetics by different groups in the country. In that workshop Professer F.A.E. Crew, a world renowned geneticist who served as an advisor to the Population Genetics and Human Development Division of the Institute, delivered the inaugural address. In his address, he stated, "In my time, I have lived and worked in many countries and have informed myself of the role that medical and social services were playing in each of them. I have gained the firm impression that in respect of social aims all nations are pursuing the same goal, are moving along the same road, though they move at different rates and are at different points along the road. It seems to me that the degree of development that these services have attained in any country at the present time and the role they play in plans for the improvement of the condition of the people are to be seen as a particular stage in the common process of evolutionary development of human societies. That which occurred in one country half a century ago is happening in another country today and will certainly take place in yet another country in the foreseeable future. So that to travel in space, as I have done, is to journey also in time."

At the end he mentioned, "This Workshop provides the opportunity for the creation of a group that can represent the geneticists and cytologists of India and that can state authoritatively what their sciences have to offer to those whose interests include the advancement of medicine as an instrument of social policy. I choose to regard this Workshop as an event of considerable importance."

Since the organization of the first workshop, long 15 years have passed. During these years considerable development has occurred in the field of medical genetics and human population genetics in the country. The subject area for discussion in the present workshop is human population genetic studies and their relevance to health care. The population genetic studies have been carried out mostly in the universities and in selected specialized institutions. Through these studies lot of information has been generated, but very little thought has been given to the potential use of this information for

human welfare. In most of the situations, the available information has been collected by the investigators without much interaction and collaboration with the potential users in the medical and health fields. Now the time has come to ponder in retrospection as to how much and in what way the available knowledge could be utilized for the preventive and promotive health care of the population. It would be agreed by all that the ultimate aim of generating knowledge should be for its utilization in human welfare. In the Alma Ata Declaration of 1978, it has been pledged to provide "Health For All" by 2000 A.D. Our country is a signatory to this declaration.

The genes, which are the carriers of hereditary codes, do not function in isolation but in the background of environment and other genes. It is well known that the quality of life is dependent upon the interactions between genetic endowment and environmental conditions, the latter being influenced by physical, nutritional, socio-economic, cultural and other factors. Obviously, therefore, any meaningful population genetic studies cannot be carried out without taking into proper consideration these important variables. All diseases are to certain extent genetic in etiology and pathogenesis, and these can be viewed as falling on a spectrum with regard to relative importance of genetic and environmental factors. At one end of the spectrum genetic factors dominate as the cause. At the other end of the spectrum non-genetic environmental factors dominate. At the present moment, the incidence of communicable diseases and nutritional disorders in our country is very high and understandably, their control would assume high priority. But with the increasing control of these environmental factors, the relative importance of purely genetic and genetico-environmental disorders will gradually increase. For meaningful intervention in this field, reliable data base should be available. Therefore, this workshop would like to consider, whether available information in the field of population genetics are dependable and comparable in terms of techniques and methodology used, and whether these are suitable, appropriate and adequate for use in preventive and promotive health care. If there are deficiencies, what is necessary to be strengthened to fill up the gaps? What type of collaborative efforts would be needed to carry out such studies? What lessons can be derived from the available knowledge and experience for the medical and health practioners and administrators? What information and in which form it may be utilized for education of the public and orientation of medical and health personnel? These are some of the aspects which need to be discussed under each topic.

I am confident that you will have very interesting deliberations and discussions during these four days of the meeting.

Inaugural Address

PROF. H. D. TANDON

Director, All India Institute of Medical Sciences, New Delhi

I feel privileged to participate in the inaugural function of the workshop on "Population Genetics and Health Care". I feel it is most appropriate that this workshop should be concerned with the current status, role, significance and application of population genetics to health care.

Man's body, his mind, his physical and mental well-being, are all products of the interactions between his inheritance and the environment he encounters in the course of his life. The human body like that of any living organism owes its structure to the interactions of many genes. A change in any of these may affect the normal functioning of the organism and such changes can be inherited.

The science of genetics, including human genetics, has been making rapid progress and the past half entry has witnessed the gradual transition of genetics from the Cinderella status of mendelism to its modern concept, which, in this field of human genetics includes population genetics, biochemical genetics, medical genetics, serological genetics and cytogenetics.

The structure and the function of the gene involves not only the individual carrying it but also the family in which it segregates and the populations in which it exists, and here lies the importance of population genetics. The interplay of forces, which determine the incidence of inherited traits in a population, needs further investigation by population geneticists. The human gene pool is profoundly affected by changes in environmental condition as well as changes in the mating behaviour of different human populations. This results in changing the frequencies of different genetic constitutions which are primarily responsible for the biological basis of the health of populations.

The vast and varied country that India is, a ready-made laboratory is available for population geneticists. It has population groups of varying sizes, endogamous caste groups, tribes and religious communities inhabiting different ecological settings. It is of paramount importance that collaborative efforts should be made by population geneticists to examine the current status, identify gaps of knowledge, delineate priority areas of research which have direct relevance to the promotion of health care in the form of preventive and promotive measures.

In this context, the application of the theory of human genetics including population genetics to human welfare is a field full of possibilities in regard to man's personal health and to the future shaping of his society. One of the main tasks of human genetics is to extend the frontiers of our knowledge about the part played by the genetic factors in health and disease. The application of the theory of human genetics to mankind has added a new dimension to diagnosis and therapy. Since population control is the country's primary concern, the general health of the people is of utmost importance.

The growing practical importance of hereditary anomalies and diseases is largely due to the fact that many exogenous causes of disease have been brought more and more under control. This has led to an increase in the relative frequency of patients who suffer from diseases in which at least some genetic component is involved. Knowledge of hereditary diseases is important not only because they present serious problems of public welfare, but also, because in an increasing number of cases an adequate therapy is becoming impossible, unless the anomaly has been diagnosed correctly at proper time.

It is now well recognised that the occurrence and incidence of many diseases are regulated by genes. On the basis of available studies, it has been observed that certain hereditary haemotologic disorders like thalassaemias, abnormal haemoglobin syndromes and glucose-6-phosphate dehydrogenase (G-6-PD) red cell enzyme deficiency etc. are present in relatively high frequency among different population groups of India. These haemotologic disorders are problems of considerable public health importance as they produce haemolytic anaemia of varying severity.

Genetic markers specially blood groups and HLA antigens play a significant role in health and disease and need further investigation for effective health care.

Marriages of blood relatives or consanguineous marriages gives rise to certain increased risks in the offspring. These risks arise both for traits controlled by recessive genes and those which are determined by polygenes. In either case, the result is to expose a proportion of the otherwise largely hidden component in human genetic variability. This proportion is substantial enough to matter. As consanguinity is fairly high in

India, specially in South and among Muslims and tribal groups, greater attention need to be paid in this direction for reducing genetic burden of the community.

India is predominantly characterised by two major sections of the population, that is, tribes and castes. Exploratory studies have revealed that there are fairly high frequencies of genetic disorders like sickling, thalassaemia, G-6-PD, colour blindness, etc. among various tribal groups and also among lower caste groups. Urgent attention is required for detailed population genetic studies among various groups for developing necessary preventive and promotive components of health care.

Information on the incidence of various congenital malformations, monogenic, polygenic or multifactorial disorders in the Indian population groups is scanty. Consequently, the estimation of risk figures for the recurrence of disorders in the family poses a difficult problem. It is imperative to generate baseline data on the incidence of genetic disorders in Indian population groups to facilitate the genetic counsellor in prediction of the extent of risk of recurrence. Such data are essentially required for the effective planning and implementation of genetic counselling services in the country, for the prevention of genetic disorders, imparting genetic education and promotion of health care.

I hope the present workshop will address itself to important genetic problems of Indian population groups and will bring forth specific recommendations having relevance to promotion of health in the form of preventive care and other measures.

Valedictory Address

COL. B. L. RAINA

Former Director, National Institute of Family Planning, New Delhi

I have great pleasure and privilege in addressing this meeting of experts. It was long ago that I attended similar meetings—in March, 1966, a seminar on reproductive biology with a session on genetics, and in March 1967, a workshop on medical and human population genetics, both held in this Institute* under the able direction of Dr. Somnath Roy.

I find that great deal of work has been done since the last workshop was held and an all India picture is clearly emerging, though large gaps still remain to be filled. I have great admiration for workers in this field who must be working under difficult conditions and meagre resources. The holding of this workshop is timely and the title "Population Genetics and Health Care" is very significant. The title underlines the fact that population genetics is within the framework of Alma Ata Declaration 1978. This is important, as there continues to be a lack of sensitivity to some basic facts that diseases of genetic origin make a major contribution to human mortality and morbidity; since the factors affecting human growth and development (from conception through various stages of human life cycle) are rooted in genetic information contained in the zygote and its environmental variables. Our serious concern in population and family planning and quality of life implies that children should be free from diseases and disorders arising out of genetic and environmental factors. Knowledge about epidemiology of these disorders is essential in health care planning.

I may recall some of the observations in the Alma Ata Declaration and the report of the Working Group on Health for All by 2000 A.D. and relate them to some of the

*Earstwhile National Institute of Family Planning

observations that I find in the recent publications on the subject. The questions may be raised; does population genetics fit in this scheme? Are the genetic diseases posing health problems? The information on prevalence of diseases of genetic origin throughout India is still far from complete. In some areas/populations studied, percent frequency of genetic disorders is very high, e.g. frequency of sickling in some parts is over 30 percent. High frequency areas and population groups obviously come under Alma Ata framework. I understand that incidence of genetic diseases in India is estimated to be around six per 100 births i.e. over a million with genetic diseases are added every year. This calls for gathering further information.

For many years I have been looking forward to emergence of computerized genetic register at this Insitute and its linkage with National Health Statistics and extension of epidemiological studies. I have no doubt in my mind that genetic diseases will come into prominence earlier than many anticipate, as the communicable diseases are controlled and environment improves. The swing in morbidity, for example, in blindness from the environmental causes to genetic causes as observed in developed countries will be seen in India. There is need for immediate action to include genetic diseases in health care in high prevalence geographical regions and ethnic groups to extend studies for getting an all India picture and also take action to meet the future needs in the long term perspective.

As follow up of this workshop, you may consider preparing all India map showing high risk areas based on availabie studies and make an assessment of delivery of services and referral facilities, including manpower and training needs. A deeper look can be taken on the needs for strengthening the population genetic centre at the national level, i.e. in this institute and at the state levels which can be developed as specialised centres/hospitals. The Working Group for Health for All by 2000 A.D. has recommended that "In order to have the best utilisation of limited specialised institutions in the country the government should seriously consider declaring certain institutions exclusively for referral services". Consideration should be given for selecting some institutions for population genetics. These institutions can be strengthened with appropriate clinical, laboratory and diagnostic facilities including cytogenetics, biochemical and biostatistical services.

A great deal of work lies ahead. Transd-isciplinary teams will be required to provide insights in socio-medical phenomena in all its complexity. Appropriate number of field teams will be needed for carrying out investigations in selected areas. Before undertaking such investigations, pilot studies may be needed to evaluate and compare screening methods and adopt a standardised methodology. The population to be screened has to be understood and techniques and methods of approach to the population needs development lest investigations boomarang and create more problems than they solve.

Areas of basic research have to be identified. I need hardly emphasise that basic research today is applied technology and research tomorrow.

Training, guidance and supervision are essential ingredients of any plan, especially in human population genetics, and provision of genetic counselling services, which are immediately needed in known high prevalence disorders. I may again repeat the need of inter-disciplinary approach. Such an approach should not merely be co-ordination but working as a constellation. Constellation approach emphasises feeling of partnership and inter-dependence.

These are some of my random thoughts I have ventured to place before you. My purpose will be served if you work them out in further detail for promoting activities in the field of Population Genetics and Health Care.

Background Papers

Abnormal Haemoglobins in India : A Critical Appraisal with Particular Reference to Promotion of Health

NEELAM MAKOL, S. K. BASU

Department of Population Genetics and Human Development
National Institute of Health and Family Welfare, New Delhi

Available information on various facets of human haemoglobins and their variants, normal and abnormal, has remarkably enriched different disciplines of modern science. The implications of different haemoglobins have interested not only clinicians and haematologists but also biochemists, anthropologists and geneticists. The Indian subcontinent is a rich reservoir of various abnormal haemoglobins which include S, D, E, J, K, L, M and Q, thalassaemias and hereditary persistant foetal haemoglobin.

Haemoglobin S (Sickle cell Haemoglobin)

This is the most commonly found abnormal haemoglobin in India. Severe and often fatal anaemia occurs when the Hb S is in a homozygous condition (Sickle cell anaemia). But in the heterozygous state, it results in the asymptomatic sickle cell trait. In India, sickling has been reported mostly from the tribal groups and lower caste communities.

Southern India

The percentage frequency of sickling ranging from 0.5 to 34.43 has been reported from Southern India. Highest frequency is found among Paniyans of Nilgiri Hills, Tamil Nadu (34.43 percent) (Lehmann and Cutbush 1952 a & b). The lowest frequency has been reported among Todas of Nilgiri Hills, Tamil Nadu (0.5 percent) (Saha *et al.*

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1976). Sickle cell haemoglobin associated with thalassaemia has been reported from Andhra Pradesh (Reddi and Baruah 1964, Reddi *et al.* 1966 and Sita *et al.* 1969).

Western India

The frequency of sickling in Western India ranges from 0.02 percent to 30.6 percent. Highest frequency has been reported from among Sorathis (30.6 percent) (Mittal *et al.* 1962) and the lowest from among Parsis of Gujarat (0.02 percent) (Undevia, 1973). Hospital cases of sickle cell haemoglobin associated with thalassaemia have been reported from Maharashtra (Deshmukh and Sharma 1968, Desai *et al.* 1968, Uma Rao *et al.* 1969). Some cases of haemoglobin S have been reported from Maharashtra by Sur *et al.* 1968; Magotra and Phadke 1975; Parekh 1957, etc.)

Eastern India

In Eastern India the frequency range is from 1.7 percent among Santhal tribe of West Bengal (Kate *et al.* 1975) to 29 percent among Griza Oriahas of Assam (Dunlop 1957). The reports of haemoglobin S associated with thalassaemia have come mostly from West Bengal and Assam.

Central India

In Central India, the frequency ranges from 1.38 percent among Mehtar of Malwa, Madhya Pradesh (Kumar 1968) to 38.21 percent among Mahar of Bastar, Madhya Pradesh (Negi 1971). Cases of Hb S associated with thalassaemia have been reported from Orissa (Praharaj *et al.* 1959). The highest frequency is among Konda paroja (13.3 percent) (Das *et al.* 1967). The frequency of sickling among aboriginals of Chotanagpur has been found to be 8.3 percent (Karan *et al.* 1978).

Northern India

Very little work has been done in Northern India covering Jammu and Kashmir, Punjab, Haryana, Uttar Pradesh, Rajasthan and Delhi. In North India, frequency of sickling ranges from 1.4 percent among the unknown community of Mirzapur, U.P. (Kiran Ganju, 1972) to 23.64 percent among Garasia of Sirohi, Rajasthan (Quoted by Negi, 1971). Case reports of sickle cell haemoglobin have come from Uttar Pradesh (Quoted by Chaterjea 1966).

Haemoglobin D

Haemoglobin D is a beta chain variant and was first reported in a Sikh soldier in Hoshiarpur District of East Punjab (Bird *et al.* 1955). Cases of haemoglobin D have been reported from Punjab and U.P. (Saha and Banerjee 1965, Gupta *et al.* 1972, Pande *et al.* 1972). Haemoglobin D associated with thalassaemia has been reported from among the Sikhs of Punjab and Sindhis of Jaipur, Rajasthan (Dutta *et al.* 1972; Jain *et al.* 1970). In Eastern India, 9 cases of Hb D in Bengalees from West Bengal and

13 cases of Hb D in unknown caste from Assam have been reported (Quoted by Chatterjea, 1966) Saha *et al* 1973.

Cases of Hb D and Hb trait in Western India have been reported from Bombay, Maharashtra (Shanbhag and Bhatia *et al.* 1976). The Goan population of Goa are reported to have 0.3 percent of Hb D trait (Lessa and Desai, 1955). In South India, except a few isolated cases of Hb D from Mysore (Swarup *et al.* 1959), Tamil Nadu (Chandrasekhar *et al.* 1974) and Kerala (Jain *et al.* 1970).

Haemoglobin E

The highest frequency of Hb E in Eastern India has been reported from among Totos of Assam (19.8 percent) followed by Meitei Manipuris of Manipur (10.0 percent) (Chaudhuri *et al.*, 1964 and Chakravarti, 1978) and the lowest from among Kaoras of West Bengal (0.98 percent), (Das *et al.* 1974). Case reports of haemoglobin E have come from Assam and Andhra Pradesh (Sinha *et al.* 1973 and Reddy *et al.* 1978). Hb E in association with thalassaemia has been reported from Bombay (Sukumaran *et al.* 1961) and Andhra Pradesh (Laxman *et al.* 1970). Except Bengal and Assam, the frequency of Hb E in other parts of India appears to be very low. In many regions detailed investigations have not yet been carried out.

Haemoglobin J

The first instance of HbJ, a beta chain variant, in an Indian was found in a Gujarati woman (Raper, 1957). Cases of HbJ and trait have been reported among Bengalees of West Bengal; Lohana community of Bombay, Maharashtra; Harijan family of Nagpur, Maharashtra and Cutchi Lohana of Maharashtra (Swarup *et al.* 1963, Sanghvi *et al.* 1958, Subedar *et al.* 1961 and Bhatia *et al.* 1976). The frequency of HbJ has been found to be 0.82 percent) among Cutchi Lohanas of Bombay. Hardly any study has been reported from South India.

Haemoglobin K, L, M and Q

The presence of Hb K was first reported from an East India family (Ager & Lehmann, 1957 a). Subsequently, instances of Hb K were reported from among Bengalees of West Bengal (Swarup *et al.* 1963) and from Southern India (Vella, 1962).

Haemoglobin L, a slow moving abnormal haemoglobin, was first reported from London in a Punjabi (Ager and Lehmann, 1957 b). Eight instances of Hb L were reported by Sukumaran *et al.* 1959 among Lohanas in Bombay. The frequency of Hb L in Cutchi Lohanas, Halai Lohanas & Mixed Sindhis of Bombay, Maharashtra, have been found to be 0.82 percent, 0.86 percent and 1.43 percent (Shanbhag and Bhatia, 1974). Hardly any study has been reported from South India, North India, East India and Central India.

Haemoglobin M was first detected in a Punjabi family living in Amritsar. Haemoglobin M in a Muslim Khoja was reported in a case with father and all four children being carriers of this trait (Bajaj *et al.* 1973).

Haemoglobin Q was reported in three Sindhi families from Bombay (Sukumaran and Vengsarkar 1972) and also from two unrelated Sindhi families (Chouhan *et al.* 1973) and from Goa (Lessa and Desai, 1955).

Thalassaemia

It was suggested by Itano (1957) that a reduction in the rate of globin synthesis was responsible for the condition called thalassaemia. This hypothesis was extended by Ingram and Stretton (1959) suggesting that this condition was of two main types : one affecting the rate of synthesis of beta chain, beta thalassaemia and the other affecting the rate of synthesis of alpha chain-alpha thalassaemia. Several workers have now confirmed this by measuring the rates of synthesis of the alpha and beta chains in virto in patients suffering from thalassaemia (Heywood *et al.* 1964, Bank and Marks, 1966, Weatherall *et al.* 1965, Bargellesi *et al.* 1968). The defect of chain synthesis is genetically determined and is associated with alterations in the haematological indices, the red cell morphology and the proportions of the minor haemoglobin components of the cell (Hb A_2 and Hb F). Thus, the two commonly found thalassaemias are beta thalassaemia and alpha thalassaemia. Both alpha and beta thalassaemias may exist either in the heterozygous or in the homozygous state.

Beta Thalassaemia

The first instance of thalassaemia in India was recorded by Mukherjee (1938) in a Bengali boy. Later instance of thalassaemia were reported from Bombay, Nagpur, Gujarat, Maharashtra, Goa, Calcutta, Kerala, Andhra Pradesh, Bihar, Orissa, Delhi, Punjab, Rajasthan, Uttar Pradesh etc. Beta thalassaemia in combination with haemoglobin variants such as D, E, S and J have also been reported.

In North India the frequency of thalassaemia trait has been found to be 15 percent in Bhanushali community (Mehta *et al.* 1971), in Eastern India it is 3.7 percent among Bengalees of West Bengal (Chatterjea *et al.* 1957 b). In Western India, it ranges from 0.88 percent to 17.24 percent : the highest being reported from Halai Lohanas of Bombay, Maharashtra and the lowest from Gaud Saraswats of Manglore (Bhatia *et al.* 1976). In South India, the frequency of thalassaemia trait has been found to be 0.6 percent among random population of Kerala (Pillay and Krishna Das 1972.)

Alpha Thalassaemia

There are two clinical forms of Alpha thalassaemia, (a) haemoglobin Bart's hydrops syndrome and (b) haemoglobin H disease, the former due to the poly-

merization of the excessive gamma chains to a tetrameric form Hb γ_4 and the latter due to the excess of beta-chains resulting in β_4 tetramer. A case of Hb H thalassaemia has been reported from Calcutta (Chatterjea, 1961). Two cases of Hb H disease from Western India have been reported (Parekh *et al.* 1967, Chouhan *et al.* 1970). Haemoglobin Bart's to an extent of 2.4 percent was detected in cord bloods from Bengal (Swarup *et al.* 1965). Hb Barts was reported from among Kayastha, lower caste and Non-Bengalees of Calcutta (Das *et al.* 1973), 0.5 1.11 and 1.59 percent respectively. In a study of cord bloods in Bombay, 0.86 percent of Hb-Bart's was observed (Sukumaran, Unpublished observation).

Hereditary Persistence of Foetal Haemoglobin

Foetal haemoglobin which froms the bulk of haemoglobin during the last two trimesters in intrauterine life, is sometime found to be high even in adult life. It is believed that in these cases the normal process of switching off the gamma-chain production and turning on the beta-and zeta-chains fails to occur. When switching mechanism fails, a high level of foetal haemoglobin continues in adult life unassociated with anaemia. Cases of hereditary persistence of foetal hemoglobin with beta thalassaemia have been reported in a Christian family (Sukumaran *et al.* 1959) and in two Bengali families (Chatterjea, 1966). Similar cases have been recorded by Barkhan and Adinolfi (1962) and Bird *et al.* (1964). Hb E along with hereditary persistence of foetal hemoglobin has been reported from Bombay in a Maratha Family (Sukumaran and Vengsarkar, 1962).

Programme Implications

Data as are currently available on the distribution of abnormal haemoglobins are not adequate to permit any definite conclusion about any possible correlations between these genetic disorders and environmental factors. Many communities have not still been studied. Among the hereditary haematologic disorders, thalassaemias and abnormal haemoglobins are problems of considerable public health importance as they produce haemolytic anaemias of varying severity. Since thalassaemia and abnormal haemolobins produce varying grades of haemolytic anaemia, there is a need to study their present state of distribution in India among various ethnic groups. This would be useful with a view to evaluating the nature and extent of selective forces operating in a population so that necessary effective steps could be taken from public health point of view.

Clinical Effects of Haemoglobinopathies

(World Health Organisation, Technical Report, September 1966)

Homozygous disorders

(a) Sickle cell anaemia : It presents as a severe haemolytic disorder. There is

considerable variability in the life span of patients with this disorder. It has been suggested that G-6-PD deficiency may confer protection against the clinical effects of homozygous sickling state.

(*b*) *Hb C disease* This gives rise to a mild haemolytic anaemia. Many patients appear to live out a full life span.

(*c*) *Hb E disease* It varies in severity from an asymptomatic state to a mild haemolytic anaemia. Under conditions of stress, more severe anaemia may occur.

2. Heterozygous disorders

(*a*) *Sickle cell trait* Splenic infarction during high altitude flight in non-pressurized aircraft has been reported. Haematuria without any other cause occurs occasionally. In addition to haematuria, hyposthenuria occurs in subjects with sickle cell trait. Urinary infection in pregnancy is increased. The complications of sickle cell trait are rare and that mortality and morbidity in affected subjects are perceptibly different from those in subjects without this trait.

Mixed disorders

(*a*) *S-C disease* Thrombosis have been reported to be more common giving rise to haematuria and aseptic necrosis of femoral head. Vascular abnormalities of retina are common. Maternal mortality after delivery is common.

(*b*) *S-D disease* It is rare and milder form of sickle cell anaemia.

(*c*) *S-E disease* It is also rare and similar to, but milder than, sickle cell anaemia.

Thalssaemias Disorders

Alpha Thalassaemia

(a) Homozygous Alpha Thalassaemia : It is lethal and results in hydrops foetalis.

(b) Heterozygous Alpha Thalassaemia : Newborns with increased Hb Bart's in the cord blood develop hypochromia and microcytosis.

(c) Hb H disease : It is a mild to moderate haemolytic disease. Patients suffer from fatigue, hepatosplenomegaly, frequent infection and fever.

Beta Thalassaemia

(a) Homozygous Beta-Thalassaemia : The children have marked splenomegaly and occasional fever and have bony abnormalities. It is very unusual for children to reach adult life.

(b) Heterozygous Beta Thalassaemia Hyperbilirubinaemia and splenomegaly may occur in more sever forms of disorder but are unusual. There is no change in the life span of individuals.

(c) *Heterozygotes for beta thalassaemia and abnomal haemoglobins*

(i) S—Thalassaemia This is a serious haemolytic disease, accompanied by enlargement of the spleen.

(ii) C—Thalassaemia and E—Thalassaemia : Patients are chronically ill, have hepatosplenomegaly, repeated respiratory infection, frequent bouts of fever and intermittant jaundice. Severity of anemia is variable. Infections and minor illness may induce crises that may cause death.

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Glucose-6-Phosphate Dehydrogenase Enzyme Deficiency in India : Prevalence and Public Health Implications

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Glusose-6-phosphate dehydrogenase is an important enzyme of the red blood cells and its deficiency is inherited as an X-linked trait. Males who carry the gene show full expression, but expression in female heterozygotes varies widely. Glucose-6-phosphate dehydrogenase enzyme deficiency is one of the most common defects of inherited red cell enzyme which renders individuals vulnerable to drug induced haemolytic anaemia. Deficiency of enzyme concerned in red cell metabolism results in sensitivity to sulpha and antimalarial drugs such as primaquine phosphate. More than 150 million people are known to be suffering from this defect all over the world, thus exerting a great strain on the preventive facilities of public health departments.

Investigations in India have shown that the frequency distribution of the G-6-PD enzyme deficiency is seemingly, connected with the prevalence of falciparum malaria. It has been suggested that G-6-PD deficiency confers some resistance to falciparum malaria and this has stimulated surveys in various populations under different ecological settings.

Distribution in India

The distribution of Glucose-6-phosphate dehydrogenase enzyme deficiency among various populations and in different states of India (the frequency of Gd gene) may be briefly stated as follows:—

Western India

Considerable heterogeneity in G-6-PD enzyme deficiency exists in this region. High frequencies of G-6-PD deficiencies have been reported by different workers among Parsis of Maharashtra, i.e. 19 percent (Baxi *et al.* 1961), 17.3 percent (Kate *et al.* 1975), 15.7 percent (Baxi *et al.* 1969), 12.3 percent (Undevia, 1973). A very high frequency of 20 percent G-6-PD deficiency has been found among Sindhis of Maharashtra (Quoted by Aggarwal *et al.* 1974). Gonds of Nagpur also show a high frequency of 17.30 percent (Solanki *et al.* 1967). Next higher frequencies of G-6-PD deficiencies have been found among Warlis and Madia 17.00 percent and 14.14 percent respectively (Kate *et al.* 1978 and 1980); Cutchi Bhanushali 12.2 percent (Quoted by Aggarwal *et al.* 1974); Katkaris 9.54 percent (Kate *et al.* 1978); Punjabi Khatris and Sindhi Lohana 8.14 percent and 7.68 percent respectively, (Shanbhag and Bhatia 1974 and Bhatia *et al.* 1976); Komatis 6.06 percent, (Mutalik *et al.* 1974) etc.

Low frequencies have been reported from among Mahars 0.5 percent, (Parikh *et al.* 1969), Chitrapur Saraswats 0.99 percent (Shanbhag and Bhatia 1974 and Bhatia *et al.* 1976), Jains of Gujarat 2.80 percent (Baxi *et al.* 1969), Cutchi Lohana 3.17 percent, (Shanbhag and Bhatia 1974 and Bhatia *et al.* 1976), Nandiwallas 3.97 percent, (Quoted by Aggarwal *et al.* 1974) etc.

Southern India

Only a few studies are reported from South India. A high incidence of G-6-PD deficiency has been recorded among tribals of Thailavarum of Andhra Pradesh 13.00 percent (Meera Khan 1964). Next higher frequencies have been found among Kurumba of Nilgiri Hills, Tamil Nadu 12.5 percent Saha *et al.* 1976), Koya of Venkatapuram, Andhra Pradesh 11.90 percent, (Goud and Rao, 1975) and Irulas of Nilgiri Hills 9.0 percent (Saha *et al.* 1976).

Low frequencies have been recorded among Syrian Christians of Kerala 1.0 percent (Baxi *et al.* 1973), Hindus of Andhra Pradesh 1.3 percent (Meera Khan, 1964), Siddis of Hyderabad 2.66 percent, (Dashratham and Rao, 1978), Andhras of Vishakhapatnam 4.4 percent, (Veerraju *et al.* 1976), etc. Case reports have been received from Pollavarm, Karnataka (Kothari *et al.* 1974).

Eastern India

A high frequency of G-6-PD deficiency has been reported from among Angami Nagas (males) of Nagaland 23.06 percent (Seth and Seth 1971); Santhals 14.3 percent, (Kate *et al.* 1975), hospital children of Orissa 11.0 percent, (Praharaj *et al.*

1977), Nepalis 8 percent (Chatterjea, 1966) etc. Next higher frequencies have been reported among Mandigas and Yadavas of Nellore and Chittoor District, 6.25 percent, 4.92 percent respectively (Hari and Ramachandraiah 1980). The frequency of G-6-PD deficiency has been found to be 5 percent among Bengali Hindus of Calcutta, West Bengal (Swarup *et al.* 1961).

Northern India

Uttar Pradesh presents a heterogenous picture of enzyme deficiency, intra-group differences among Brahmins and non-Brahmins have been reported. A very high frequency of enzyme deficiency 30 percent has been recorded among the Sindhi patients of Agra (Kalra *et al.* 1973). Mittal *et al.* (1967) reported 6 per cent of G-6-PD deficiency from Agra, U.P. and Ahmad *et al.* (1972) reported 11.1 percent from Allahabad.

CLINICAL EFFECTS OF G-6-PD DEFICIENCY

Different variants of G-6-PD deficiency produce different clinical effects. A (−) subjects and B (−) subjects produce the following clinical effects (*W.H.O. Tech. Rep. Ser. No. 338, 1966).*

(a) *Favism* It is the most serious consequence of G-6-PD deficiency and may result in death. It is a severe haemolytic anaemia which results from ingestion or other contact with the fava beans and perhaps with other closely related legumes. It is common in younger boys and it occurs primarily in the spring. The attacks of favism appear to be sporadic.

(b) *Neonatal hyperbilirubinaemia* G-6-PD deficiency has been found to be associated with hyperbilirubinaemia in Itlay, Greece and in East and South East Asia but it does not appear to be associated with hyperbilirubinaemia in Israel. A high percentage of newborns with pyknocytosis have been found to be G-6-PD deficient.

(c) *Drug induced haemolytic anaemia* G-6-PD deficient subjects are especially sensitive to the haemolytic effects of a large variety of drugs. The most commonly used haemolytic drugs are nitrofurantoin and the 8-aminoquinoline antimalarials. Especially, in case of 8-aminoquinoline antimalarials, administration of a haemolytic drug to a patient who is known to be G-6-PD deficient may be injurious.

(d) *Haemolysis induced by infections* Infections, particularly with viral agents appear to precipitate haemolysis in subjects with G-6-PD deficiency.

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Blood Groups and their Association with Diseases

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Introduction

The health of a community, generally, is measured in terms of diseases reduction. Natural history of the disease brings out clearly that disease is caused by multiple factors, which may be related directly or indirectly, to the man and his environment. These factors, in any case disease can be biological, nutritional, chemical, physical, mechanical, environmental, social, economical, cultural, psychological, human behavioural and genetical. In this regard the question of possible association between the genetically determined markers within the blood and specific diseases has received significant attention in human genetic research. Several comprehensive genetic studies between various diseases and disorders have already been undertaken and ABO blood groups polymorphism provides for the most extensively studied erythrocyte marker.

Blood Groups and Diseases

A possible association between blood groups and diseases, when established, will provide important clues towards understanding the specific biological function and its use as a diagnostic tool to delineate the degree of susceptibility of the individuals to invasion by various parasites. Cases of established association may help towards interpreting the characteristic geographical distribution of some of the numerous genetic polymorphisms determined in human blood.

It has been realized (Vogel *et al.* 1960, Damian 1964, Cavalli-Sforza and Bodmer, 1971, Bodmer and Cavalli-Sforza 1976, among others) that cross reacting substances

similar to blood group antigens are present on the cell walls of a number of pathogenic organisms, e.g., E. coli, and S. typhymurium, and might in fact determine susceptibility of the individuals to invasion by such pathogenic organisms.

Global Perspective

A good deal of work has been done throughout the world on the association of diseases, viz., neoplastic diseases, infective diseases, abnormality related to pregnancy, ulcers, diabetes mellitus, mental disorders, rheumatic fever, rheumatic heart diseases, disorders of circulatory system, with ABO blood groups. Mourant *et al.* (1978) have effectively compiled the worldwide data on the relationship of diseases with blood groups.

The overall global perspective of the association of diseases with blood groups presents the view that the frequency of blood group A individuals is substantially higher than those with blood group O and B among the patients with cancer of pancreas, stomach, pernicious anaemia, carcinoma of colon, rectum, breast and bronchitis. Further, the individuals with blood group O are found to be more susceptible to peptic and duodenal ulcers. Among the asthma patients, there is a marked preponderance of blood group B. There is fairly strong evidence that diabetic men show an excess of group A, whereas diabetic women show significant differences from the control series. It has also been observed that patients with pulmonary and non-pulmonary tuberculosis show a high frequency of blood group A and O. However, in other infective diseases the findings are variable.

Studies in India

In India, a large number of reports are available attempting to correlate the blood group with diseases. Most of these have remained inconclusive. A summary of the available studies showing some association is given in Table 1.

Table 1

ABO BLOOD GROUPS AND DISEASES : ASSOCIATIONS WITH SPECIFIC BLOOD GROUP

Disease		*Authors*	
Asthma	Marked preponderance of group B as compared to control	Anand, S.	(1964a)
Eosinophilia	An increased incidence in groups A and B	Anand, S.	(1961)
Pulmonary Tuberculosis	A and B Blood group distributions in the pulmonary tubercular patients and control do not differ significantly.	Sidhu *et al.*	(1974)
Pulmonary tuberculosis	A very high frequency of blood group O was observed in pulmonary tubercular patients. No statistical test was done to confirm the result.	Laha and Dutta	(1963)
Syphilis	Result are inconclusive. Negative results were obtained for patients with war+ & war− test in the primary and secondary stage of syphilis whereas in tertiary stage there exists an association between syphilis and blood groups—frequency of tertiary syphilis has been found to be higher especially in group B individuals.	Vogel and Helmbold, *C. F.* Seth and Seth	(1971)
Small Pox	A and B more frequently and more severely affected than B and O. The disease may take a milder course in carriers of blood group B and O.	Chakravarti et al. and Vogel and Chakravarti	(1966)
Renal Lithiasis	A high incidence in persons of group A than in persons of Group B and AB.	Seth and Seth, Anand	(1971) (1964b)
Vitiligo	More common in Group B	Srivastava and Shukla	(1965)
Leprosy	A high frequency of group A+AB as compared to B+O in leprosy Patients.	Jay Raj *et al.*	(1980)
	Findings inconclusive	Chakravartti, M. R.	(1971)

Contd.

ASSOCIATION WITH SPECIFIC BLOOD GROUPS

Disease		*Authors*	
Acute Myeloid Leukaemia	One case of a patient with B Blood group suffering from this disease due to some modification of B antigen.	Undevia *et al.*	(1966)
Infective Viral Conjuctivitis	Frequency of this disease is highest in group A	Agarwal *et al.*	(1975)
Filariasis	More frequent in patients of group O and B.	Anand, S.	(1965)
Duodenal Ulcer	O group persons are found prone to the disease.	Dharmaraju *et al.*	(1971)
Pre-eclamptic Toxaemia	B group persons are found prone to the disease.	Dharmaraju *et al.*	(1971)
Cancer of Cervix	Preponderance of group A among those affected with cancer of cervix.	Dharmaraju *et al.*	(1971)
Diabetes Mellitus	An excess of blood group O among the Diabetic patients.	Chakravarti, M. R.	(1973)
Small Pox	Incidence of small pox was found to be much higher in patient with blood group A and AB.	Chakravarti, M. R.	(1966)
Skin Diseases	Subjects with blood group A are more prone to the various skin diseases and this susceptibility decreased in that order with groups AB, O and B. urticaria, alopecia aereata, pyoderma, fungal infections, acne vulgaris and zoster were significantly common in group A while infective eczema, erythema multiforme, contact dermatitis, psoriasis and vitiligo in group AB subjects.	Hajini *et al.*	(1975)
Congenital Heart Disease	ABO and Rh (D) blood groups of 133 patients of Congenital heart disease were examined. A high frequency of Rh negative cases (9.02 percent) has been observed in the patients where as in the control the frequency is only 3.7 percent.	Bhatnagar & Sidhu	(1977)
Chicken Pox	A blood group is more frequent among the patients Persons with group A (probably of AB too) have somewhat higher risk than persons with groups B and O.	Chakravarti and Chakravarti.	(1977)

Contd.

ASSOCIATION WITH SPECIFIC BLOOD GROUPS

Disease		*Authors*	
Vitiligo	Comparison of 1000 unrelated vitiligo patients with 2000 blood donors has shown a significantly reduced risk in the case of the O blood group and apparently a higher incidence of vitiligo in individuals with blood group A and B.	Kareemullah, L. *et al.*	(1977)
Tuberculosis and Diabetes	Group A shows highest frequency 36 percent in the case of tuberculosis while in the case of diabetic patients blood group O shows highest frequency (42 percent)	Bhosale, N. and Kulkarni, V. S.	(1977)
Rheumatic Fever	The blood group A was found to be in 14 percent, B in 39. 5 percent, while another 17.8 percent had blood group AB, the remaining 28.7 percent were found to have blood group O. Significantly large ($P < 001$) number of rheumatic children were found to have blood group AB.	Ahmad, S. H. *et al.*	(1978)
Cholelithiasis	The material comprises 321 patients regarded as suffering trom gallstone against a control of 688 collected from the general population. An increased frequency of blood group A compared to blood group O in the patients was observed suggesting a significant association.	Chakravartti, M. R. & Chakravarti, R.	(1978)
Filariasis	Data on 125 filariasis patients (37 males and 88 females) and 100 controls (60 males and 40 females) were collected. It has been found that the distribution of ABO blood groups are not different among the patients and the control groups,	Subramanyam, K. and Ramachandriah, T.	(1978)
Ascariasis, Cataract, Corneal Ulcer, Tuberculosis, Diabetes and Bronchial Asthma	Considering the proportions of all the diseases together occuring in the Badaga patients, it was found that 47.65 percent of them belonged to O group as compared to 31.25 percent of normals with an excess of 16.40 percent. But in Toda patients blood groups other than O shows higher prevelence compared to the controls.	Reddy, V. R. et al.	(1978)

Contd.

ASSOCIATION WITH SPECIFIC BLOOD GROUPS

Disease		*Authors*	
Jaundice, Filariasis and Diabetes mellitus	No definite relationship between the occurence of jaundice and ABO phenotypes was found. Similarly no definite relationship was found between the occurence of filiariasis and ABO blood groups. A possible relationship was found to exist between the occurence of diabetes mellitus and ABO phenotypes. The diabetic patients tend to show an excess of A phenotype among them (16.11 percent).	Ramachandraiah, T. et al.	(1978)
Respiratory Diseases.	Three sets of blood groups viz; A : O, B : O and A+AB : B+O were taken into consideration for comparing the patients with asthma and chronic bronchitis with the control group. The Chi-square value obtained for the last set (A+AB : B+O) was highly significant (X^2=9.197) suggesting some degree of involvement of blood groups in these diseases.	Sehajpal, P.K. et al.	(1978)
Mental Retardation	No asscciation of ABO blood groups has been found with mental disorders.	Chakravartti, R., and Roy, A. K.	(1980)
Cancer of Cervix Oesophagus and Cheek	Women with blood groop B than with group A or O are more susceptible to be affected with cancer of cervix. Patients with cancer of Oesophagus also tend to show an excess of group B phenotype.	Ramachandraiah' T. et al.	(1981)

Programme Implications

Associations of various diseases with blood groups are still tentative, either in India or elsewhere in the world. Yet the importance of such associations in human health is extremely vital. A functional explanation for the association of the particular blood group with certain diseases is required for promulgation of preventive and promotive health care. It is therefore, necessary that research programmes are carried out with extreme precision so as to arrive at conclusions which could be effectively utilised in heaith care.

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HLA Antigens and Diseases

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Introduction

Leucocytes are perhaps the most convenient, easily obtainted, source of human living nucleated cell and their antigens have been studied as being representative of the individual that bears them. As early as 1931, Landsteiner had emphasized the parallel between the problems of matching for blood transfusion and transplantation and advocated for blood groups for matching in tissue transplantation. On these lines, Gorer (c.f. Bodmer 1978) discovered the major histocompatibility system, H-2, in mouse, matching for which had a significant effect on the survival of transplanted tumour. Later on, Snell (1948) confirmed the importance of H-2 antigens in the transplantation. The H-2 system has served as an important model for study of HLA system in man.

Early studies of HLA system in man have depended on population and family studies, using the human red cell blood group systems as a model. Rood and Payne (1958) discovered that the leucocyte agglutinins were produced by fetal-maternal stimulation. Using such sera, Rood (1962) defined a two-allelic system designated as 'group 4'. Later, Payne *et al.* (1964) defined an apparantly independent allelic system which they called LA (L for leucocytes and A for the first locus). Subsequently, extensive research on the HLA system in man during past 20 years has resulted

in a rapid development in knowledge of HLA system and in proliferation of the known HLA specificities. So far, three serologically defined loci, i.e.,-A, -B, -C, one leucocyte defined locus, -D, and three serum complement factors, the C2 and C4 of the classical and factor B of the alternative pathway have shown to be coded for by the genes in HLA region on the short arm of chromosome number 6 (Bodmer 1978).

The four HLA loci, i.e., -A, -B, -C, -D,/DR reveal astonishing degree of polymorphism as compared to serum complement factors. At least 90 different alleles are known to be present at HLA -A, -B, -C, and D/DR loci.

Due to complexity of antigens it was important to have a common agreement on nomenclature. Precisely for this reason, the committee of World Health Organization coined the term HLA, meaning H for human/histocompatibility with L for leucocyte, the cell type first studied and A for the first system and not for the antigens (C.F. Bodmer, 1978). Thus, to describe a whole system it was agreed to use letters for the loci which prefix HLA.

Nature of Antigens

The HLA-A, -B and -C antigens are glycoproteins, consist of a light chain (mol. wt. 12,000) beta microglobulin, which is coded by a gene on chromosome 15 and a heavy chain (mol. wt. 43,000) which bears the antigenic determinants that confer HLA specificity on the molecule and is the product of the HLA -A, -B and -C loci and which is located on short arm of chromosome number 6.

Inheritance

Because man is normally diploid, individuals can carry no more than two antigens for each locus. The HLA antigen combination determined by the genes on one chromosome is known as the haplotype and is normally transmitted from parent to offspring as a unit in a simple mendelian way.

Cross-reactions between HLA, -A, -B, and -C antigens

Stimulation of an individual with HLA antigen of a single foreign specificity will often produce antibody not only against the stimulatory antigen but also against related specificities. This may reflect the complexity of the antigens and the presence of a number of antigenic determinants, some of which are shared by more than one specificity. Most antisera available have a dominant specificity but also react to a lesser extent with other cross-reacting specificities. Cross-reaction is also shown in absorption studies in which

antibody may be absorbed from serum, not only by the stimulating antigen but also by antigens cross-reacting with it. The antigens within each allelic series show a large amount of cross-reactions but there is little, if any, between the series. Barnstable *et al.* (1971) have reported some of the cross reacting groups of -A and -B series.

Importance of HLA and tissue transplantation

In human beings, the influence of matching donor and recipient antigens of HLA system on the outcome of tissue allografts is confined mainly to renal and corneal transplantation. Regarding renal transplantation, Festenstein et al. (1971) were first to identify significant differences between poorly and well matched donor and recipient combinations on the basis of matching for limited number of antigens at HLA -A and-B locus of HLA system. Immediately after this, the advantage of matching HLA antigens was seen all over the world (Dausset *et al*, 1974, Morris 1975, Festenstein *et al.* 1976, Walker *et al*, 1977 among many others). A very important aspect of matching in clinical transplantation is the determination of specific donor pre-sensitization in the recipient. Furthermore, minor histocompatibility systems must also influence graft survival, especially in senstized patients.

The clinical value of matching for HLA in renal transplantation is slowly being placed into its correct perspective. Exact matching for the whole HLA region can substantially improve results as is shown by experience with related donors. But in common clinical situation, where a donor is an unrelated cadaver, complete matching for just the HLA -A and -B loci alone is a difficult task, even with large lists of prospective recipients. Even if all antigens at these two loci are matched, there are HLA -C, -D and DR loci to be considered. The HLA-D locus fortunately appears to be of little importance, but the role of HLA -D and DR is still doubtful. Nevertheless, HLA -A and -B loci have been shown to play significant role in renal transplantation.

Matching for HLA antigens have been shown to result in a better graft survival in corneal transplantation (Batchelor , 1976., *et al.*, Kissmeyer-Nielsen *et al*, 1977, Gibbs *et al.*, 1978). There is not much information about matching for HLA in transplantation of other tissues, except for bone-marrow transplantation. Information on skin allografts, cardiac and liver transplantation is still fragmentry.

HLA as Population Marker

Because of highly polymorphic nature of HLA system its importance in population studies is yet to be defined clearly. A limited number of studies have been carried out

to study the distribution of HLA specificities in the different population groups of the world (Bodmer and Cavalli-Sforza, 1976, Joysey and Wolf, 1978, Sochnev *et al.*, 1981, Lokki and Julin, 1982, Reisner *et al.*, 1983 among etc.). Most of the studies relate to the the distribution of HLA -A, -B and C loci. Bodmer and Bodmer (1978) have reported the distribution of HLA gene frequencies in the three major human racial groups. They have reported a high frequency of 27 percent of A 2 aliele in Caucasoids, 37 percent of A 9 allele in Mongoloids and 22 percent of AW 30 allele in Negroids. Regarding the B locus, they have observed that allele B 7, B 12 and BW 35 occur more or less in the same proportion (ranging from 9 percent to 16 percent) in Caucasoids. However, Mongoloid ethnic group is characterized by a high frequency of B5 and B40 alleles (around 22 percent), on the other hand, Negroid racial group shows a characteristic frequency of Bw 17 allele and blank allele (around 17 percent). Further, Cw4 and Cw6 alleles are found to occur in similar frequency (around 12 percent) among Caucasoids. Mongoloids are characterized by a high frequency of Cw3 allele (around 27 percent) whereas Negroids are characterized by a relatively high frequency of Cw6 allele (around 17 percent). However, the frequency of blank allele has been found to be more than 45 percent in all the three groups at C locus. Joysey and Wolf (1978) reported similar observations on the distribution of HLA antigens among the different population groups of the world. Recently, Mathews *et al.* (1981) reported cell typing of 293 unrelated individuals of North India for HLA -A, -B and -C loci. They found that they show more affinities with Caucasoid than with Mongoloid population groups.

HLA antigens and diseases

The highly polymorphic HLA system in man has proved a useful marker in certain diseases. HLA system plays a significant role in the success of organ transplantation and platelet transfusion. A number of studies are now available (Thorsby *et al.*, 1973, Vladutiu and Rose, 1974 among many) enumerated the association of HLA antigens with variety of diseases. Such associations have proved the utility of HLA antigens as useful tools in understanding the susceptibility and predisposition of individuals to various diseases. In brief the available information regarding the association of HLA antigens with various diseases is given in Table 1.

Global perspective

Amiel (1967) was first to report the association of second series antigen "4C" of HLA system with Hodgkin's Lymphoma, which was later confirmed by Kissmeyer-Nielsen *et al.* 1971, Morris and Forbes, 1971, Thorsby *et al.* 1971. This antigen was found to represent a group of HLA-B locus antigens, now recognized as B5, BW 35, B18 and B15. However, the most striking association is that between Ankylosing Spondylitis

Table - 1 Relationship Between HLA and Disease : Empirical Risk

Disease	Associated HLA antigen	Frequency of antigens		Relative Risk
		Controls	Patients	
Ankylosing Spondylitis	B 27	8.6*	89	90.1
Acute anterior Uveitis	B 27	8.6	47	9.4
Rheumatoid arthritis	Dw4	19.4	48	3.9
Multiple Sclerosis	Dw2	25.8	60	4.3
Myasthensis gravis	B 8	23.7	56	4.1
Coeliac disease	Dw3	26.3	96	73.0
Dermatitis herpetiformis	Dw3	26.3	83	13.5
Chronic autoimmune hepatitis	Dw3	26.3	71	6.8
Sicca syndrome	Dw3	26.3	87	19.0
Indiopathic Addison's diseases	Dw3	26.3	76	8.8
Grave's disease	Dw3	26.3	61	4.4
Insulin dependent	Dw2	25.8	00	00
Diabetes	Dw3	26.3	48	2.5
	Dw4	19.4	49	3.9
Subacute thyreoiditis	Dw35	13.1	72	16.8
Psoriasis Vulgaris	Cw6	33.1	88	14.9
Idiopathic haemachromatosis	A3	26.9	73	7.4
	B14	4.5	19	5.0
C-2 deficiency	Dw2	—	—	—
Reiter's Syndrome	B 27	8.6	77	35.9

c.f. A. Svejgaard and L.P. Ryder (1979). *Percentage

(a form of rheumatism causing lower back pains) and the antigen B 27 (Brewerton *et al.* 1973, Sachs and Brewerton, 1978).

HLA Antigens and Arthropathies

The B 27 association, with AS in various population, has been found to be more than 90 percent in Caucassion and 50 percent in American Negroes (Khan *et al.*, 1977 Ruderman and Ward, 1977). Sasazuki *et al.* (1977) reported an incidence of 67 percent of B 27 in patients with AS. Further observations on HLA system in AS patients indicate that HLA-B7 may also be associated with the development of AS in the B 27 negative patients (Khan *et al.* 1977 b). It is worth mentioning here that reiter syndrome, yersina and salmonella arthropathies, psoriatic arthropathy, frozen shoulder syndrome are also found to be associated with HLA B 27 (Bulgen *et al.* 1976).

HLA antigens and Endocrinological and other disorders

It has been observed that dermatitis herpetiformis, gluten sensitive enteropathies, juvenile diabetes mellitus, hyperthyroidism and Addison's disease show a common association with HLA-B8 antigen (Barnetson *et al.* 1973, Asquith *et el.* 1974, Nerup *et al.* 1974, Grumet *et al.* 1973, Thomsen *et al.* 1975). In some of these conditions other antigens are also found to occur in increased frequency. Svejgaared et. al. (1975) and Cudworth and Festenstein (1978) reported an increase in HLA-Dw3 and Dw4 in juvenile diabetes mellitus and Nerup *et al.* 1977 reported an increase in B 18 in the same diseases. In Japan, thyroid disease was found to be associated with an increase in Bw 35 (Konishi *et al.* 1976). However, HLA antigens in leprosy have provided variable findings (Thorsby *et al.* 1973, Smith *et al.* 1973, Kreisler *et al.* 1974, Reis *et al.* 1974).

HLA antigens and Leukaemia

Some tentative associations have been reported between HLA antigens and acute Inmphocytic leukaemia (Thorsby *et al.* 1969, Walford *et al.* 1971, Harris *et al.* 1978). The antigens most frequency implicated are A 2 and B 12.

HLA antigens in Carcinoma and Tumors

In some malignant diseases, particularly the nasopharyngeal carcinoma and oesophageal carcinoma, relatively close associations with HLA have been described Nasopharyngeal carcinoma has been reported in association with an increased frequency of HLA Bw46 among Chinese and Mongoloid people (Simons

et al., 1974, Simons *et al.* 1975). Recently, Hall *et al.* (1982) reported associations between Bw 44 (in possible combination with Aw 36) and resistance to both Burkitt's lymphoma and nasopharyngeal carcinoma; and between B w45 and long-term remission in nasopharyngeal carcinoma. Kinsman *et al.* (1983) found that the presence of HLA-DR 3 was associated with nasal carriage of staphylococcus aureus.

Similarly, oesophageal carcinoma has been found to be associated with HLA-B 40 in Turkish people (Simons and Amiel, 1977). Haemochromatosis, a disorder of iron storage, has a very close association with A 3, B 14 and B 7 (Shewan *et al.*, 1976, Simon *et al.*, 1976 Bomford *et al.*, 1977). Idiopathic haemochromatosis and active hepatitis, the two liver diseases, are found to be associated with A 3 and B 8 respectively (Eddleston and Williams, 1978). Libby *et al.* (1983) found an increase in the frequency of B-cell allo-antigens, HLA-DR 2 in patients with idiopathic pulmonary fibrosis.

The associations involving multiple sclerosis, which is a very distressing progressive degenerative nervous disease, are particularly interesting. There is a relatively slight, though undoubtedly significant, increase in the antigens A 3 and B 7 in people with this disease. There is, however, a very marked increase in the frequency of D 2, which is an allelic product of another gene in HLA (Jersild *et al.*, 1973; McDevitt and Bodmer, 1974, Batchelor *et al.*, 1978).

Among the patients with coeliac disease the frequency of B 8 was found to be more than 85 percent and psoriasis, the frequency of B 17 was found to be increased considerably (McDevitt and Bodmer, 1974). In pursuing the study of HLA antigen associations, all the initial work was based on typing for the serological determinants of the HLA-A and-B loci. As increasingly sophisticated techniques became available for the detection of allelic products of other loci, studies have been extended to include HLA-C,-D and,DR antigens. Recently, Ungar *et al.* (1981) found an increase in-DR 2 and -DR 4 and a decrease in DR 3, HLA-DR patterns in the patients with pernicious anaemia as compared to the controls.

Studies in India

In India, only a few studies have been conducted regarding the distribution of HLA antigens in different population groups and their association with various diseases.

Using old nomenclature Raha (1975) reported the distribution of HLA antigens among the Bengalees of Eastern part of India. A high frequency of allele 1,2 and 3 was observed at LA locus and 5,7 and 8 at locus 4. Bale *et al.* (1980) found a high frequency of allele A1, A2, A9, All and A 24 at locus A and B 7 and Bw 35 at locus B in 118 normal individuals residing in Bombay. Recently, Mathews *et al.* (1981) reported the cell typing of 293 unrelated individuals of north India for HLA-A,-B and-C loci and

found that they show more affinities with Caucasoid then with Mongoloid population groups.

Association of HLA antigens with diseases in India

Mehra *et al.* (1976) found a significantly decreased frequency of HLA-A9 antigen in the non-lepromatous leprosy compared to the lepromatous group of Western India, These observations corroborate the results of their early study of HLA and susceptibility to leprosy conducted in Delhi (Das Gupta *et al.*, 1975). Bale *et al.* (1980) reported a very high incidence of 82. 5 percent of B 27 antigens in patients with ankylosing spondylitis. A high frequency of HLA-B 27 in patients with AS has also been reported from North India (Sen Gupta *et al.* 1977). Malaviya *et al.*, (1979) also found an increased frequency of B 27 antigens in patients with sero-negative spondoarthropathies. in India. Sen Gupta *et al.* (1979) reported a high incidence of HLA-B26 in acute uveitis in north Indians, which was further confirmed by Mehra *et al.*, (2983). However, Mathew etal, (1983) could not conclusively find HLA linkage to congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

Programme Implications

An interesting feature of most of the diseases associated with HLA is that they appear to be connected with abnormal immune response antigens, and henceforth come into the category of auto-immune related disorders.

It would be worthmentioning that HLA antigens have shown a remarkable degree of association with diseases, e.g., ankylosing spondylitis, coeliac, disease and also significant importance in acceptance or rejection of tissue grafts particularly the renal and corneal transplantation. HLA antigens have a direct relevance in saving many human lives and providing preventive and promotive care in variety of diseases which otherwise would have been extremely difficult.

It seems probable that HLA linked immune response genes and genes with other related function will be shown to be important genetic factors predisposing to resistance or susceptibility to variety of cancers, auto-immune disorders and infectious diseases in man, which will utimately help in better preventive and promotive health care.

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Genetico-Environmental Studies Among the Tribal Population of India : Consideration of Approaches for Promotion of Health Care

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Tribes

The tribal population groups of India are known to be the indigenous autocthonous people of the land. References in the epics of *Nishadas*, *Dasyus*, *Kiratas*, *Shudra*, *Dravidas* and the available linguistic evidence suggests that they were inhabiting the riverbanks and plains. (Risley 1901, Grigson 1931, Elwin 1939, Majumdar 1961). They had a food gathering economy, lived in isolated settlements and shelters at various levels of constructional activity, belonged to different physical types and had primitive religion. Invaders such as Aryans, Greeks, Romans, Mongols, Sakas, Arabs, etc. brought with them a typical tempo of growth, an advanced articulate language and they gradually brought in the concept of Samiti, Parishad, Sabha and Kingship and were able to evolve a distinct socio-religious system, which is often referred to as the Hindu Brahmnical system. They developed an economic system based on production managed by the hereditary principals which has come to be known as caste system (Chatterjea 1968). Exponents of the Hindu Brahminical system because of their dominant position harassed the origininal dwellers and forced them to move into the deeper inaccesible terrains of the land. Evidence suggests that they were able to maintain their cultural heritage and identity and individual socio-economic set up (Vidyarthi 1977). Attempts to mix with the other population groups often resulted in their assimilation in the Hindu Brahmnical system at the low heirarchial status. Tribals are often referred to as

Vanyajati, Adimjati, Vanwasi, Janjati, etc. but are most commonly referred to as *Adiwasi* or *Anusuchit Janjati,* the latter being the constitutional name.

Distribution

There are about 427 recognised scheduled tribal groups in India constituting approximately 7.5 percent of the total tribal population of the country (Roy Burman 1971). They vary widely in number and concentration in different regions of the country. The tribal areas can broadly be divided in seven regions (Sharma 1978). The Southern Central region comprising Madhya Pradesh, Southern Orissa, Eastern belt of Andhra Pradesh, is mainly inhabited by Gonds. The Central Northern Region including Chotanagpur tribal belt of Bihar, Eastern Madhya Pradesh, Northern Orissa, Western tribal region of West Bengal, shows the highest tribal concentration dominated by *Santhal, Oraon, Munda,* etc. The Western Tribal region covering Southern tribal belt, of Rajasthan, Eastern tribal belt of Gujarat, Western belt of Madhya Pradesh, Northern Maharasthra, Dadra Nagar Haveli and Daman has the predominant tribal groups of Bhils, Gamit, Dhodias and Warli. Eastern Tribal region comprises of Hilly areas of Assam, Meghalya, Arunachal Pradesh, Sikkim, North West Bengal and plain areas of Assam and Tripura, has tribal groups of *Bhotias, Naga, Khasi, Moro, and Miri, Mompas,* etc.

The North Western Tribal region extends from Hills of Western U. P. and Northen Himachal Pradesh where Lahaulis, Jaunsaris and Kinnaura are the major tribal groups. Southern Tribal region covering Tamil Nadu, Karnataka and Kerala has tribal groups of *Soliga, Kurumba, Malyali,* etc. The Oceanic group represents the tribal communities such as *Jarwas, Onge's, Great Andmanese* and *Sentinelese* in Andaman, Nicobar and Lakshdweep.

The distribution of the tribal groups shows that they inhabit widely varying geoclimatic conditions. The degree of availability of forest and land resources also varies considerably which in turn dictate the economic set up of the tribal groups.

The emphasis of research studies has been primarily on socio-cultural aspects of tribal life. Recent researches have tried to unravel the process of social change, economic aspects, and other dimensions revolving around the tribal ways of life. Tribal population groups of India are characterised by their individual, cultural, religious, social and economic lineage through which they have been able to maintain their separate entity as distinct from other population groups and even their fellow tribesmen (Vidyarthi and Rai 1977). In strict biological sense the tribal groups are distinct biological isolates.

(a) Medico-Genetic Problems Among the Tribal Groups

Environmental conditions and socio-economic factors including a wide gamut of variables like mating pattern, preferential alliances, age at marriage, income, occupation, nutritional status, education, climatic conditions, do affect in some measure the medico-genetic profile including genetic and non-genetic disorders of the population groups. Genes provide a template for development and the final phenotype is the result of interaction between heredity, the genes, and environment. It is imperative to study independently the purely genetic disorders, resultant disorders of the interaction between genotype and environment and those governed by environmental agents. Genetically, a population can be defined as a breeding or a potentially interbreeding group of individuals which determines, the overall genetic constitution of the population group. Population size, available array of genotypes, the relative fitness of the genotypes, their ability to produce and survive do affect the transmission of the genes. Selection, mutations, migration etc. are the other important inbuilt components of the genetico-environmental studies.

The various factors which determine or contribute to the ultimate population structure, including social, cultural, economic, nutrition and genetic factors, are listed below.

Socio-economic Status

Distribution of the tribal pockets in India speak volumes of the wide variety of geo-climatic habitat, available agricultural land, forest reserves etc. which govern the sustenance of their economy. Review of the ethnographic notes periodically published by the Registrar General, Census of India, and a compendium of social science reports point out that the tribals of India are basically agriculturists, their technique of agriculture still in the primitive stages, abhoring the use of implements because of their faith and concern for the mother earth. Forest produce, live stock farming, fishing, etc. in general contribute to their income. In some tribal groups, e. g. Nagas, promotion of the traditional craftsmansnip has been augmented to supplement their economy. Despite the efforts of the Government, literacy rate is between 5.7 percent among the tribal populations. (Sharma 1978, Census 1971), Lushais with the literacy rate of approximately 50 percent are an exception. Studies on the European and Indian population groups have brought forth evidence of the impact of socio-economic status on fertility, mortality and morbidity rates. However, it has to be reiterated that effects are operated through the awareness about the medical facilities, approach, belief, and response to the medical system, religious and cultural taboos,

availing of the facilities, better nutrition, etc. Hardly any systematic studies have been carried out on the Indian tribal groups to estimate the impact of the socio-economic concomittants on fertility, mortality and especially morbidity aspects. Such information is essentially required to understand the magnitude of the problems and plan the inputs required for the promotion of health and family welfare programmes.

Nutritional Problems

Among tribal population groups staple diet is rice, except Mompas of Assam who consume wheat also. Birds, fish and other meat products are also consumed by tribals. Studies carried out at National Institute of Nutrition (1971) and Planning Commission of India (Sixth Five Year Plan, Government of India) reported a high protein calorie malnutrition along the rice-eating belts. Studies available on the dietary status and health of the tribals of Bihar and Maharashtra observed deficiency of their diet in calorie as well as protein and essential amino acids content though, major signs of nutritional deficiencies were not observed (Chitre 1976). Similar results were obtained from the studies among the pre-school tribal children of Andhra Pradesh (Rao *et al.* 1977) and tribals of Kalahandi, Koraput, Madhya Pradesh and Maharashtra (Pingle 1976). Surveys on the nutritional deficiencies (Gopalan 1971) among the tribals reported a high incidence of goitre, angular stomatitis among the Mompas of Assam and Vit. A deficiency among the Onges. Data on the nutritional deficiency disorders among the other tribal groups is scarce. It must be kept in mind that nutritional status is directly correlated to the economic status of the group. To evolve a suitable strategy to overcome the nutritional deficiencies among the tribals and promulgate preventive and promotive health care, the various socio-economic concomittants and cultural variants have to be taken into consideration.

Mating Pattern

Individual socio-cultural practices, religious customs and geographic locations resulted in close breeding among tribals. Almost all tribal groups practice endogamy with varying degrees of inbreeding and parental consanguinity. In Andhra Pradesh, a high frequency of consanguinity has been reported among Koya Dora, Konda Reddis, Pardhans (above 50 percent) and 20.50 percent among Rajgonds (Chakravarti, 1969). Ghosh (1976) reported 12.69 percent frequency of consanguineous marriages among the Kotas of Nilgiri hills. A very high percentage frequency of parental consanguinity (59.4 percent) has been reported among the Gonds of Madhya Pradesh (Yadav, 1968) and among the Bhils (59.20 percent) of West Khandesh (Karve, 1957). Regarding the preferential marital alliances, frist cousin cross marriages are sanctified and religiously

practiced in most tribal groups, while uncle niece marriages are also practiced in some tribal groups of Southern India. The data with respect to frequency of consangunity and preferential marriage alliances on large number of tribal groups are still not available. However, the present available data suggests a higher frequency of consanguinity and inbreeding as compared to the caste Hindus, Christians and Muslim groups of India (Malhotra 1978).

If the present trends of consanguinity are some indicators, it is imperative to study the effects of inbreeding and parental consanguinity in terms of the reproductive wastage, pre-reproductive mortality, congenital malformations, etc. almong the tribal population groups. Ghosh (1976) has elucidated the genetic load increase among the Kotas of Nilgiri hills of Andhra Pradesh due to frequent still births, abortions, etc.

Polygamy is practiced among many tribes of Eastern and Central regions of the country. According to census 1961, 15.25 percent of all marriages among the tribals were polygamous. It has been a matter of dispute whether polygamy contributes to the frequency of infertility among tribal groups. Comprehensive studies on polygamy, its incidence, reasons for practicing polygamy and implications thereof are yet to be undertaken.

Pregnancy and Child Birth

The foetus is prone to damage by a large number of intra-uterine and extra-uterine factors namely, maternal age, maternal disabilities like diabetes, hypertension, previous child bearing experience, maternal nutrition, antigenic sensitivities, infection, etc. Beside that, the cultural taboos, etc. may also contribute to the damage to the foetus or neonate. Attainment of puberty heralds marriage among the tribals which renders them more prone to frequent abortions, stillbirths and neonatal mortality, the effects being compounded by the increasing birth orders and the known genetic antigenic sensitivities like Rhesus factor and ABO incompatibilities. Data on the Rhesus factor shows a low frequency (3 percent) among the tribals and in some population groups it is altogether absent (Bhalla 1966, Majumdar 1977), however, the ABO blood group gene frequencies vary widely in various tribal groups. Maternal infections during pregnancy by viral agents like toxoplasmosis, rubella, etc. may result in permanent handicap in the form of mental retardation and blindness. Vitamin and nutritional deficiencies during pregnancy do contribute to the avoidable intrauterine growth retardation, physiological and mental welfare of the child. Relevant data on the tribal population groups in this connection are hardly available.

Fertility and Mortality

Implicit in the discussion on the medico-genetic problems among the tribals it is important to know the fertility and mortality status among the various tribal population

groups. There is very little information on the fertility and mortality status among the tribal populations. Both biological and cultural factors affect the fertility status of an individual. Driver (1963) studying the fertility differentials in Central India reported an early age at marriage among Gonds (13.5 years for females) and a mean fertility of 4.8 per mother. A very high mortality 41.7 percent among the Gond mothers was observed with a mean fertility of 2.8. Bhowmick (1971) reported a very high reproductive wastage (abortions and still births, 11.65 percent) and 29.48 percent neonatal and infant mortality among the Zemi women of Nagaland. Ghosh (1976) reported similar findings among the Kotas of Nilgiri Hills, alongwith moderately high (17.4 percent) incidence of infertility. The tribal groups are distinct biological isolates characterised by their individual socio-economic, religious, cultural practices and indigenous health care practices, it would not be appropriate to make any generalisations depending on the available data. Detailed studies must be undertaken to obtain base line information on fertility and mortality pattern so as to evolve a suitable plan and effectively implement the health and family welfare programmes among the tribal population groups.

Genetic Disorders

Since the first description of Sickle cell trait in Southern India (Lehmann and Cutbush 1952) a large number of studies have been carried out on the Indian tribal population groups on the incidence of various abnormal hemoglobins, particularly Sickle cell trait, Glucose-6-Phosphate Dehydrogenase deficiency and Thalassaemias. Distribution of Sickle cell trait in tribal populations varies widely ranging from more than 20 percent among the Pardhan, Gamit, Paniyan, Kurumba, Irulas, Rajgonds of South Western tribal region to less than 5 percent among Lambadi, Dhurwa, Santhal, Todas, Kotas, etc. in the South Eastern tribal region. Data from a few tribal groups from Central India are also available. Despite this, the variation between the incidence of sickling from the same population groups by different authors (studies carried out at different times) proposes the initiation of a model study to understand the magnitude of the problem. Mortality among the carriers of the trait and the reproductive performance among the mothers are yet to be explored in greater details which will provide the understanding of the mechanism of selection and maintenance of the gene through reproductive compensation, etc.

Selective advantage hypothesis relating to the endemicity of malaria and the incidence of sickling in a population group is yet to be confirmed in the Indian population groups and the tribals groups provide ample opportunities for such studies. Preliminary observations among the tribal groups of Nilgiri Hills (Verma 1978) are interesting enough in conceptualising such studies.

Another red cell enzyme which has invited considerable interest is the Glucose-6-Phosphate Dehydrogenase red cell enzyme deficiency (G-6-PD). The incidence of

G-6-PD deficiency among the tribal population groups of India varies from 1-15 percent while in many tribal groups the investigators showed the absence of G-6-PD deficiency (Baxi *et al.* 1971). Its relationship with the malarial endemicity in providing a selective advantage in the carrier state, and as well the therapeutic problems it generates with the usual antimalarial drugs are well understood. Investigations on the alternative methodology of treatment and the preventive and promotive measures to be adopted to avoid the clinical embarrasment remain on the priority list of the health and welfare measures.

The other hemoglobin abnormalities like Hb, D, HbE, HbQ, HbJ, are yet to be explored on the tribal blood samples. Few overall studies have been reviewed (Sukumaran, 1978). In the discussion on the promotion of health among the tribals the necessity for carrying out such studies is implicit. Thalassemia is another hemoglobin anomaly which should be explored among the tribals in greater details. Another dimension is the co-existence of various hemoglobin abnormalities with thalassemia often referred to as thalassaemia syndromes, possibly, resulting in the increased mortality rates (Subba Rao *et al.* 1968, Sukumaran 1978) in terms of foetal wastage and child mortality. The most important fallacy in carrying out such studies on large scale is the absence of simple screening techniques.

(b) Population Trends among the Tribal Groups of India

Census of India is the organisation entrusted with the gigantic task of enumeration of the people of the country. The diversity of the problems of enumeration, e.g. the language, geographical location of the inhabitations, transport, ethnic groups, literacy, etc. and of course the time factor are bound to be reflected in the limitations of the data for which certain adjustments are always justified. The duration between the two census periods, i. e., a decade provides sufficient time period to estimate reliable growth rates for the population groups of India. Tribal population accounted for 6.94 percent of the total population of the country in 1961 census while it was 7.5 percent in the 1971 census showing a growth rate of 26.0 percent during the decade 1961-71 as compared to the 24.8 percent of the total population of the country.

State-wise analysis of growth rate among the tribal population show a growth rate of more than 30 percent in the States of Assam, Gujarat, Manipur, Nagaland while in Bihar and Himachal Pradesh it is as low as 17.3 and 18.8 percent respectively and

in other states it is between 20-25 percent. Tribe-wise growth rate of the population shows considerable variations ranging from 35.27 percent of Bhils to 14.5 percent of Munda. The smaller tribal groups show a highly distorted population growth picture. Some tribal groups of Andaman and Nicobar Islands show a declining trend (Verma 1977)

What are the factors reponsible for high and low population growth rates among the tribal populations? Some of the reasons can be traced back to the limitation of the census operations itself. In 1951 census, 212 tribes were listed as scheduled tribes compared to the 400 at the time of 1971 census which is duly reflected as an increase in the percentage population of the tribes compared to total population of the country. A careful study of the listing of the various tribes shows certain inclusions and exclusions with respect to sub tribes or sub groups (Sinha 1979).

Internal migration of the tribes from one region to the other contributes significantly to the variation in the observed growth rate in a particular area. Tribe-wise growth rate variations has been attributed to both factors together (i.e., enumeration problems and migration).

Any discussion on the growth rate among the tribal population groups without reference to fertility and mortality components is incomplete. A higher fertility rate with an equally high mortality rate or a low fertility rate and high mortality rate, frequency of infertility, or a high fertility and low mortality rate, etc. may substantially influence the growth rate. It is well known that the fertility and mortality in a population group is the result of interaction between the biological, cultural, socio-economic, nutritional and extent of medical facilities available on the other hand. Whatever the observation has been on the increasing and the decreasing trends among the tribal groups, the census figures for 1981 may allow some tangible conclusions on the demographic aspects and population trends among the tribal population groups.

It would be wrong to state that the genetico-environmental (medico-genetic) problems of the tribals are well understood. The foregoing discussion enumerate a few indicators of health in the few tribal population groups studied through individual efforts of the curious and venturing lot of the investigators. Comprehensive data on the medico-genetic problems among the tribals are still lacking.

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Genetic Counselling

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Human nature to understand and alleviate the sufferings of fellow human beings has resulted in development of medical sciences at a very rapid pace as compared to contemporary sciences. Utilisation of the technical advancements in the field of chemistry, physics, and engineering sciences specially electronics improved the scope of understanding and diagnosis of disease as well as therapy and treatment. Knowledge on the hereditary disorders, though well documented in the works of early physicians, has increased considerably and is fast expanding after the development of the molecular concept of disease. More or less simultaneous advent of cytological techniques to study the chromosomes, coupled with the understanding of the banding phenomenon of the chromosome have facilitated the diagnosis of a large number of birth defects. While it has been possible to diagnose the birth defects and hereditary disorders, treatment of such diseases is still a nightmarish job. Efforts for treatment and prevention of such disorders, aided by the developments in the diagnostic procedures gave rise to the concept of genetic counselling.

(a) Concept and Scope of Genetic Counselling in India

The term genetic counselling, first used by Reed in 1947, can be defined as prediction of occurrence or recurrence of a genetic disorder within a family and its communication within the framework of medical, emotional, social and religious factors. Many investigators have published their experiences and views on genetic counselling

within the framework of their individual working conditions and clientele (Bergesma 1963, Fraser 1974, Motulsky 1975, Stevenson and Davidson 1976, Lubs and delacruz 1977). In general, genetic counselling is non directive. It merely provides the medical and genetic information to the couple to make independent decisions regarding future progeny. A counseller must not force decisions lest he assumes the role of a eugenicist. Neverthless, most of the time it is expected of him of make the decision (Milunsky 1979).

The process of genetic counselling involves essentially, diagnosing and establishing the risk of recurrence of the genetic disorder; interpreting and communicating the risk to the counsellee; helping the counsellee to weigh the risk in personal terms and formulating a rational approach and follow-up of the counsellee.

Diagnosing and establishing the risk of recurrence of genetic disorder

Based on the history of the disease, physical examination, routine laboratory investigations and special directive laboratory investigations, an accurate diagnosis of the genetic disorder has to be established. Detailed family history, ethnic background, parental age, reproductive history, abortions, still births, infant mortality, its causes, sex and age, consanguinity, incidence of disorder in any other family member, and screening of the sibs and parents for the disorder to identify heterozygotes are essentially required in order to establish the recurrence risk in the family. Knowledge of the disorder, its genetics, inheritance characteristics, penetrance, prognosis and the treatment available are the inputs required from the counsellor (Milunsky 1979, Emery 1975, Cartor 1977).

Interpretation and communication of the recurrence risk

To achieve the objectives of genetic counselling, it is of utmost importance to evaluate the social and religious background of the counselle for modulation and orientation of counselling, since birth of a malformed baby is often a social stigma and suggestions of the adoption of contraceptives may be religious taboo in certain societies. Understanding the educational background and psychological response and personal needs of the counsellee is of considerable help in effectively communicating the risk of recurrence and in stimulating the decision making process. (Singh 1975, Ahuja 1975, Emery 1975, Emery 1976).

Formulation of a rational approach

Communication of the recurrence risk may invite a series of questions which are to be answered by the counsellor. The counsellor must reassure the parents couple

about the universal distribution of harmful genes to eliminate or reduce the anxiety or guilt complex. Genetic education must be imparted to create a positive awareness. Counseller should initiate discussions on the future options about the progeny, suggest contraception and inform them about the possibility of prenatal diagnosis.

Follow-up of the counsellee

Follow up of the counsellee helps in reassuring the couples, sometime in recognition of mistakes, if any, and creates the possibilities of future research and benefiting them of the recent developments.

Scope in Indian Context

Indian population groups are characterised by different ethnic, socio-cultural, socio-economic and religious backgrounds. Our knowledge about the existence of the various genetic disorders is limited mainly to the case reports, generating from the hospital data. Limited diagnostic facilities at the peripheral levels, almost nonexistent recording system, poor referral system, besides illiteracy, socio-cultural and religious myths, taboos, are major factors responsible for the lack of information on genetic disorders. In India, there is an urgent need of the development of proper genetic counseling services. Along with each hospital a genetic counselling centre should be started for imparting effective genetic education, prevention and management of disorders and finally ensuring optimal health to the people.

(b) Empirical Risk Estimates and Genetic Counselling in the Indian Context :

Genetic counselling basically aims at prevention of the recurrence of the genetic disorders in the family and as such in the society. The knowledge of genetic disorders in the human populations has expanded, with the advanced diagnostic procedures having helped in the finer differentiation and understanding of the causative factors in diseases having similar manifestations. Thus importance of an accurate diagnosis preceding the prediction of risk figures is increased. To arrive at an accurate diagnosis the genetic heterogeneity of the disorder has to be resolved. Approximately 1489 autosomal dominant traits and 1117 autosomal recessive and 205 X-linked traits are

known (Mckusick 1978). Our knowledge of the genetic disorders is based on the studies carried out in western population groups, through chance observations and study of isolates, etc. More data are available on simple mendelian traits which have a better chance of being recognised.

Resolution of Genetic Heterogeneity

At the time of physical examination of the patient the detailed genealogy, age at onset of the diseases, screening of the sibs of affected individuals, if any, is of utmost importance. For example, in case of Huttington's chorea, the age at onset of the disease provides an important clue to the prognosis as well as prediction of risk figures (Wendt 1972). Corneal clouding in the case of an X-linked Hunter's Syndrome helps in differentiating the autosomal from of the Hunter's Syndrome (Mutalik 1975). Biochemical assays of the primary enzyme deficiencies, e.g. in Galactosaemia, Phenlyketoneuria, Alkptoneuria, establish the genotypic constitution of the parents as well as the affected child. In cases where primary defect is not known, the secondary enzyme changes, for example, in X-linked Duchhene Muscular Dystrophy, the creatine phosphate kinase enzyme levels are increased while the CPK levels are normal in other types of Muscular dystrophies (Shaw 1977). Linkage studies have made it possible to confirm the genetic disorder although the number of markers available is just negligible. Analysis of mode of inheritance often helps in the resolution of genetic heterogeneity (Emery 1976).

Empirical Risks

In case of monofactorial traits, the risk estimates are primarily mendelian and depend on the mode of inheritance. The examination of the sibs and parents is an inbuilt component. In case of dominant traits the penetrance and the segregation may confound the genetic counsellor but the basic principles of estimation of risk figures remain the same. Possibility of fresh mutants in case of monofactorial traits must always be kept in mind. Consanguinity in the population is another factor which should be given due considerations in estimating the risk estimates.

The mode of inheritance of approximately 60 percent monofactorial genetic disorders has been confirmed (Mckusick, 1978). Data on the Indian populations with respect to monofactorial disorders are limited to chance observations in the hospitals. Most of the information is on the traits which are compatible to life, e.g. Marfans Syndrome (Saifullah, 1967), Retinitis pigmentosa, (Basu, 1978, Grewal *et al.*, 1981) and some other syndromal conditions, e.g. Treacher Collins Syndrome, etc. (Verma, 1975).

Besides that, data on haemoglobinopathies, sickle cell gene, thalassaemia and other abnormal hemoglobins (Baxi, 1974, Sukumaran, 1978, Swarup Mitra, 1963, Chatterjea, 1957 and others) among the Indian population groups are available. However, systematic studies for the incidence of monofactorial traits in Indian population groups are yet to be undertaken.

Polygenic Disorders

The polygenic disorders are relatively common. The risk estimates for the future progeny are based on the recurrence of the disease in many affected families, i.e. population studies. In such cases usually the contribution of various genes individually is unknown. Examples are cleft lip ± cleft palate, neural tube defect ± anencephaly, idopathic epilepsy, maniac depressive psychosis, schizophrenia, etc. (Emery 1976). The risk estimates available in literature are based on the Western populations (Cartor, 1971, Shaw, 1977, Milunsky, 1979) and may not be relevant to Indian populations. Large number of reports on various polygenic disorders, e.g., cleft lip ± cleft palate (Grewal, 1976, Banerjea, 1981, Ramesh *et al.* 1981), mental retardation (Ambani, 1980, Usha Rani *et al.*, 1980, Ahuja, 1980, Chakraborty, 1980), neural tube defects (Verma, 1978, Salfullah, 1967, Mital 1969, etc.), myopia and essential hypertension (Basu, 1978, Goswami, 1980) are available. Nodal studies to evaluate the incidence of various polygenic disorders and empirical risk estimates in the Indian population groups are yet to be undertaken in a systematic manner.

Chromosal Disorders

Large number of chromosomal disorders are now known. The best illustrated chromosomal anomaly is Down's Syndrome (21 trisomy or translocation) which occurs with a fairly high frequency. Majority of chromosomal disorders are the result of nondisjunctional errors, translocations or chromosomal breaks. Estimation of the risk figures for the future progeny usually depend on the nature of the disorder, the carrier state of balanced or transient polymorphism and their reproductive fitness. Hospital based studies on the Indian populations have brought forth data on the incidence of various chromosomal anomalies, e.g. Down's Syndrome (Verma, 1975, Ambani, 1980, Rafiyudeen, 1976, Kulkarni, 1980) and other chromosomal anomalies of sex differentiation. However, detailed family studies and population studies are required to estimate the frequency of various chromosomal anomalies in Indian populations.

Programme Implications

The incidence of various congenital malformations monogenic, polygenic or multifactorial disorders in the Indian population groups is scanty. Consequently, the

estimation of risk figures for the recurrence of disorders in the family poses a difficult problem. Because of the varying genetic lineage, inbreeding and other environmental conditions, it is imperative to generate base line data on the incidence of genetic disorders in Indian population groups to facilitate the genetic counsellor in evaluating the prediction of the risk figures. Such data are essentially required for the effective planning and implementation of genetic counselling services in the country, for the prevention of genetic disorders, imparting genetic education and promotion of health care.

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